

Graphene and its Health Effect

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Abstract

This study is a review of risk-related information on graphene with the purpose of outlining potential environmental and health risks. It is a guide to future risk-related research on graphene. The study will be based on the emissions, environmental fate, and toxicity of graphene. It shows that graphene could exert a considerable toxicity, emission of graphene from electronic devices and composites are possible in the future. It is known that graphene is both persistent and hydrophobic. Although these results indicate that graphene may cause adverse environmental and health effects, and that there are many risk-related knowledge gaps to be filled with the environment. Graphene can bind the cell surface and cause physical and chemical damage to the cell membrane. It is known that graphene may interact with protein and nucleic acids, altering their structure and function on the other hand, graphene may regenerate reactive oxygen species (ROS) which can also cause disruption of membrane, lipids, proteins and nucleic acids. The toxicity of graphene should be further studied.

Introduction

Graphene is a monolayer thick, 2-dimensional form of carbon atoms linked together in a hexagonal lattice. The sp² hybridization of all bonds across the sheet gives rise to its interesting and unique, physical, mechanical, thermal and electrical properties. Thus graphene can be considered to be a 2-dimensional form of its analogue graphite. Importantly, the properties of graphene vary significantly to the bulk material graphite, particularly in terms of electron mobility, and these significant feature differences have driven research in fields as diverse as electronics, materials, energy, defense, security, water and health [1,2]. However to date, the bulk of the material that is produced is geared toward research applications or in composites production. Graphene is transparent, flexible, very strong, and has already been used to create fast transistors.

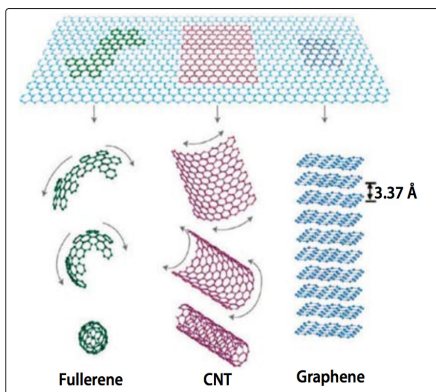


Figure 1: An illustration of different allotropes of carbon arising from a graphene sheet [3].

All carbon nanomaterial are based on variations of graphene, a one atom thick honeycomb-like arrangement of carbon atoms. Graphene can be stacked, wrapped or rolled to form graphite, football-like ‘buck balls’ or carbon nanotubes (CNTs). Research into the properties and uses of graphene has rapidly expanded over the past decade. Indeed, prior to the seminal paper by Geim, et al. which eventually led to the 2009 Nobel Prize for physics, the potential of this material was relatively underappreciated [4]. The use of graphene as the load-bearing component in composites is highly beneficial. The high tensile strength of graphene coupled with the ultra-high aspect ratios that are possible using most particulate production methods has led to the rapid uptake of this technology. Furthermore, the potential for using graphene in thin film and coatings applications is increasing, with the goal to produce modified surfaces with improved structural integrity, better heat resistance, conductance, transparency or protection from corrosion [5]. Recent studies have also shown that graphene could be used in water purification applications due to its high cation exchange capacity and its vast available surface area, it can also be use for desalination. Other potential applications of graphene include in sensor technology, opto-electronic devices, high electron mobility transistors, super capacitors, catalysis and photovoltaic (nano crystal solar cell). Many of these uses for graphene will have significant economic and environmental benefits however it is of great importance that the possible downside effects of incorporating graphene into products which may come into contact with the biosphere are accurately known. A thorough understanding of the interaction with biological material is essential prior to the uptake and utilization of graphene on a wide scale, particularly if there is significant potential for it to find its way into the environment and human body. Graphene is

an attractive material for the development of membranes due to its atomic thickness, mechanical strength and chemical stability. Pristine sheets of graphene are thought to be impermeable to all atoms and molecules. However, by forming nanometer-sized pores in the material, it can potentially act as alter, allowing molecules smaller than the pores to pass through while excluding larger species [6]. Potential biomedical applications for graphene have been suggested. The low surface energy of graphene makes it an attractive substrate for the delivery of hydrophobic drugs [7-8].

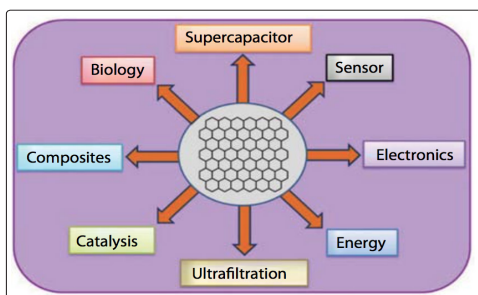


Figure 2: An illustration of various applications of graphene and its derivatives [3].

The unique structure of graphene could allow for its use as a contrast agent in biomedical imaging since the influence of particle size is important in biomedical applications. Single layer graphene may potentially sit in between the leaflets of a lipid bi-layer; it is unlikely though that few layer graphene however could be incorporated. Furthermore, the ability for cells to phagocytize graphene is largely dependent upon particle dimensions [9]. Whilst cytotoxicity is hence of a clear and present concern, graphene as a building block presents a novel opportunity for designing and functionalizing systems and products that can potentially transform the manner in which we live. Hence there is a strong push for understanding the interaction of graphene with cells and bacteria. Bacterial interaction with surfaces is ubiquitous in nature. There are also countless examples where biofilm formation leads to significant environmental and health problems. For instance in a marine environment, biofilm formation on ship hulls can lead to corrosion and increased drag as bacteria colonization can lead to subsequent attachment of other organisms such as barnacles. Whilst this can result in a substantial economic cost, the health problems arising from bacteria attachment to medical implants can be fatal if not properly dealt with in a timely fashion [9-10]. However the possible health effects of graphene are both positive and negative and it will be looked into so that the measures to reduce or cancel the health risk of graphene can be discussed.

Positive Health Effects of Graphenes

Graphene can be used for environmental applications, such as cleaning up hazardous materials and pollutants in contaminated waters. While the potential use and safety of CNTs has been investigated for some time, much less is known about graphene, partly because of early difficulties in increasing its production and because it is in an early stage of development [11]. Now, with increasing research, the adoption of different types of graphene materials in different industries will increase the likelihood of human exposure to this material. The researchers are investigating the physical and chemical characteristics of graphene as well as CNTs to look at how both may affect health [12]. Existing knowledge and experience from safety studies using CNTs was used to speculate on the safety of graphene and the possible effects of graphene on human

health should be examined at the cellular, tissue and whole body levels in comparison to CNTs. The extent and mechanism by which cells interact and uptake graphene is considered critically important, since once inside a living cell the material could interact with or disrupt cellular processes and cause damage. Exposing the body to carbon nanomaterial could result in either their accumulation in the tissues or elimination through excretion. Accumulated nanomaterial could pose a risk to organ function, and therefore to health [13].

There are two main safety factors to consider regarding exposure to CNTs and graphene. The first is their ability to generate a response by the body's immune system and the second is their ability to cause inflammation and cancer. Three generalised guidelines had been developed from the existing evidence and if implemented, could reduce the overall health risk to a minimum for workers involved in developing graphene as well as graphene-based technologies. The graphene sheets are small enough for immune cells to engulf and can be removed from the site where they were found in the body. A stable graphene sheet can be easily dispensed in water to minimise clumping and aggregation in the body and chemically modified graphene material can be cleared from or biodegraded in the body, to prevent damage from chronic accumulation into the tissues [11].

Improving the Delivery of Chemotherapy

Graphene had been used as an alternative coating for catheters to improve the delivery of chemotherapy drugs.

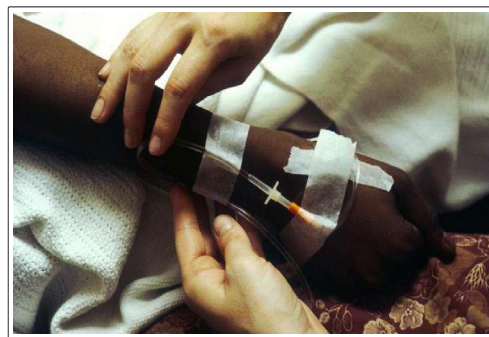


Figure 3: Use of graphene as an alternative coating for catheters [14].

The research suggested that placing graphene which is an extremely thin sheet of carbon atoms; on the internal surfaces of intravenous catheters commonly used to deliver chemotherapy drugs into a patient's body will improve the efficacy of treatments, and reduce the potential of the catheters breaking [14]. The study indicates that damaging interactions can occur between the most commonly used chemotherapy drugs, 5-Fluorouracil (5-Fu) and silver—one of the most widely used coating materials in medical applications. As a result of this damage it is believe that the drug may not deliver the desired therapeutic effect in patients, and that chemotherapy treatment may be compromised.

Moreover by-product of the reaction between 5-Fu and silver is hydrogen fluoride (HF), a strong acid, may be injected into the patient along with the treatment. Co-author of the study Justin Wells, from the Norwegian University of Science and Technology, said: "As far as we know, nobody has ever looked at the chemical reaction between chemotherapy drugs and the materials they routinely come into contact with, such as catheters and needles and their coatings. It is just assumed that the drugs are delivered into the body intact." "We

have shown that silver is catalytically degrading the chemotherapy drugs, which means they are probably not being correctly delivered into the patient. Our research indicates that one of the decay products of this reaction is HF, which would be a worrying thing to inject into a patient.” As a solution to this problem, the international teams of researchers have proposed using graphene as an alternative coating material for catheters. In their study, the researchers used a technique known as x-ray photoemission spectroscopy (XPS) to study the chemical composition of 5-Fu, as well as the drug’s reactions with silver and graphene.

XPS is a technique used to measure the surface chemistry of a particular material by firing a beam of x-rays at it and collecting the electrons that are subsequently emitted from the very top layer of the material. The researchers performed these measurements at the Swedish national synchrotron laboratory—MAX IV Laboratory. Their results showed that when 5-Fu comes into contact with silver, reactions occur in which there is a massive loss of the element fluoride from the drug, leading to the creation of HF. When the researchers with 5-Fu repeat the experiment and graphene, they found that these reactions completely disappeared and that graphene caused no damage to the drug. Graphene is a biocompatible material with low toxicity that has already been suggested as an external coating for biomedical applications.

The fabrication of thin graphene coatings is technological feasible and can even be grown on top of silver to maintain compliance with existing fabrication methods. The understanding of the critical interactions between drugs and medical coatings should be increased with a view to make the knowledge freely available for all to use.

Drug Delivery

Drug delivery systems (DDS) have been devised to minimize the side effects of bioactive drugs by restricting their functions to only the desired sites. Such systems have also been used to prolong medicinal effects or treatments. The current challenges in DDS research are developing a smart delivery system for recognized targets, which is called ‘targeted drug delivery,’ and a sustained and responsive release system for the drugs. Realization of an optimal release system will require controlling complex transport and surface phenomena (e.g., diffusion, degradation, swelling, release profiles, and adsorption of DDS elements). In this context, I project that graphene will find vast opportunities as a DDS carrier because of its exceptional versatility and functionality.

One proven strategic route is that water insoluble hydrophobic bioactive agents, can attached to the surface of a graphene by physical bonding in the forms of hydrophobic, van der Waals, or π - π stacking interactions. Graphene with bio agents may be further modified to be soluble in aqueous conditions by grafting water-soluble molecules onto them. Thus, the resulting graphene complexes could facilitate the overall efficacy of the drug. It was reported that a GO-PEG complex can be physically decorated with a water insoluble aromatic SN38 (7-ethyl-10-hydroxy-camptothecin), thus creating reservoir sites for hydrophobic drugs. Because of the extremely hydrophobic nature of graphene crystal surfaces, SN38 adhered well to the complexes, and the whole complexes showed controlled release of hydrophobic drugs in physiological serum solutions. These GO-DDS complexes would be useful for broad ranges of biomedical applications because of their safety and non-cytotoxicity, which were confirmed by in vitro cell experiments.

Having been demonstrated that the GO-Fe₃O₄ magnetic nanoparticle hybrids are suitable for DDS carriers [15]. The loading capacity of the drug, doxorubicin hydrochloride (DXR), was 1.08 mg/mg, which was much higher than all other common drug carrier materials (i.e., polymer micelles, hydrogel micro-particles, liposomes, and carbon Nano-horns). These hybrid complexes can be congregated and dispersed reversibly under different pH conditions. This pH-triggered, controlled magnetic behaviour provides a unique advantage as DDS carriers. Report on doxorubicin (DOX) loaded GO, encapsulated with folic-acid-conjugated CS, as a drug carrier [8]. This carrier showed better controlled, and prolonged, drug release after encapsulation, compared to without encapsulation. Furthermore, because the DOX were attached to GO by physical π - π interactions, release was highly sensitive to pH under physiological conditions. Intrinsic biomaterials can be used to modify graphene to be more biocompatible. Report show that gelatine wrapped graphene Nano-sheets (GNs) exhibited no cytotoxicity. In acidic environments, the complexes showed fast drug release, as well as high loading capacity under other conditions [15]. The drug delivery actions were demonstrated with complexes loaded with the anticancer drug, DOX, which killed MCF-7 cells, while other complexes without the drug did not interrupt growth of the cells. Similarly, graphene could be modified with biocompatible CS. A covalently grafted GO with CS (GO-CS), could be used as a nano-carrier of camptothecin (CPT), an anticancer drug insoluble in water. The release profile of the nano-carrier gradually increased to 17.5% for 72 h. Cell toxicity of the carrier was tested by MTT assay of human hepatic and cervical carcinoma cells (HepG2 and HeLa). While GO-CS showed no toxicity up to 100 mg/L, GO-CS-CPT showed a 50% growth inhibition concentration (IC₅₀) at a concentration of as little as 29 μ M [16].

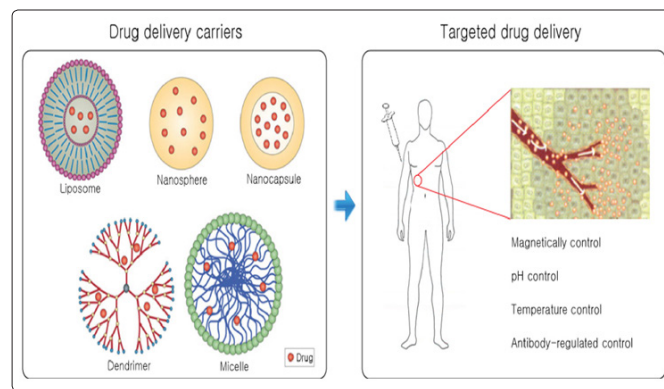


Figure 4: Schematic illustration of a drug delivery system [17]

Use for Neural Interfaces

A neural interface is a communication system between a tissue in a body and an external electrical device, which is mostly operated by electrical signals. Due to the electrochemical signals between a stiff, dry electrode and a soft, wet tissue, the challenges are not just showing good physical properties and performance, but also chronic biocompatibility and functional stability of the electrode.

A good neural electrodes must be biocompatibility to delay or avoid immune responses by the body and the cell safety must be ensure to prevent them from being damaged. Chemical or electrochemical should be stable to bear changes within the body. The electrode selectivity and sensitivity should be effective to measure electrical signals [17]. A hard, rigid and stiff materials (e.g., ceramics

and metals—platinum, iridium, and gold; silicon, and indium tin oxides), are currently used for neural electrodes, softer electronic materials are now receiving increasing attention to better adapt to the difference in interfacial qualities of cells and electrodes. Some conducting polymers, including polyaniline, polypyrrole and poly(3,4-ethylenedioxythiophene (PEDOT), showed promising results with improved biocompatibility and electrochemical impedances over conventional metals. After discovery of the limitations of functional durability of those conducting polymers after chronic implantation, carbon nanomaterials are now being investigated as new types of neural electrodes. Therefore graphene and other carbonaceous materials (e.g., carbon nanotubes) are emerging as a potential neural interface material. The graphene-coated composites significantly lowered sheet resistance and enhanced attachment of primary cortical neurons onto the scaffolds the uncoated ones. It means that high quality graphene can be used to interface with cells directly, without other biomaterials [18]. The biocompatibility of graphene can also be improved by appropriate physical treatments instead of being coated with other non-conducting biomaterials. The graphene deposited electrodes on a flexible microprobe could be used as a retina prosthesis electrode. The graphene surface can be treated with steam plasma in order to make the electrode hydrophilic as well as biocompatible. This treatment ultimately resulted in an improved signal-to-noise ratio during neural recordings from the axons of a crayfish and the heart of a zebra fish. This noise may have been caused by proximate contacts between the cells and electrodes [17].

Graphene electrodes are excellent electrochemically functional materials, particularly for sensitive recording of biological signals [19]. Measured an action potential directly from cardiomyocyte-like HL-1 cells using arrays of graphene-based transistors. The graphene-based solution-gated field-effect transistors (SGFETs) used in their work were sensitive enough to record selective biological signals, i.e., an S/N ratio of more than ten, which is analogous to a state-of-the-art microelectrode array [20]. Also designed is the graphene-silicon nanowire FETs interfaced with embryonic-chicken cardiomyocyte. These graphene-FET in contact with spontaneously beating cardiomyocyte cells provided regularly spaced peaks with a frequency of about 1.1 Hz, and an S/N ratio of more than four, for the conductance versus time measurement results [21]. GO is used as a dopant of PEDOT films for neural electrodes. PEDOT-GO exhibited a sharp decrease in electrical impedance of the Pt-Ir neural electrode. As tested the PEDOT-GO surface with primary cortical neurons, their neurites were extensively branched out, even within a day of incubation. There was no significant difference in viability between PEDOT-GO and PEDOT-PSS, but the cells on PEDOT-GO showed longer neurite length than those on the PEDOT-PSS, which is a clear benefit for application to neural electrodes. Furthermore, laminin peptide could easily be grafted onto the GO so that its coating surface showed much improved neurite outgrowth from the cells [22-23].

Negative Health Effects of Graphene Health Risk to Workers

Graphene is a two-dimensional carbon sheet that has a single atom thickness; it is receiving a significant interest due to its unique mechanical and electrical properties. It can be grown via chemical vapour deposition from carbon-containing gases on the surface of catalytic metals including Co, Pt, Pd, Ni and Fe. [23].

Studies had shown that graphene oxide in a solution mimicking groundwater clumped and sank, and this suggests that it is not a risk. But in the case of surface water like lakes and storage tanks for drinking water graphene oxide stuck to the organic matter produced by decomposing plants and animals and floated around. The mobility of water increases the chances that animals and people could ingest graphene oxide, and this shows toxicity in some early studies in mice and human lung cells [24].

Investigations on toxicity of graphene nanosheets in both Gram-positive and Gram-negative bacterial models have shown that graphene damages bacterial cell membranes through direct contact of the bacteria with extremely sharp edges of the nanowalls. When tested in the respiratory tract, the graphene caused a milder toxicity on the epithelial cells and luminal macrophages in comparison to carbon nanotubes. Particle size, particulate state, and oxygen content of graphene are key issues in its toxicity to human red blood and skin fibroblasts. It is known that graphene oxide induces cytotoxicity and genotoxicity in human lung fibroblasts through generation of reactive oxygen species and apoptosis. The functional groups density on the surface of graphene oxide sheets plays a key role in its cellular toxicity. Though it is possible to reduce the toxicity by manipulating the surface functional groups or masking the oxygenated functional groups using a biocompatible polymer or manipulating the surface functional groups [25]. The effects of graphene oxide and polyvinylpyrrolidone modified graphene oxide on human immune cells have been investigated in vitro and showed that polyvinylpyrrolidone has a lower immunogenicity than unadorned graphene oxide. Mogharabi, et al. Safety concerns to application of graphene compounds in pharmacy and medicine [26]. The modification can increase the anti-phagocytosis ability of graphene oxide against macrophages with a significant improvement in biocompatibility of graphene oxide [27]. Graphene oxide is able to induce DNA cleavage, which raises the concerns about potential toxicity of graphene oxide in human body [28]. The toxic effects of graphene on shoot and root growth, cell death, biomass, shape, and reactive oxygen species of several plants including cabbage, tomato, red spinach, and lettuce have been already investigated. The physiological and morphological analyses indicated that exposure to graphene inhibits the plant growth and biomass through overproduction of reactive free radicals [29].

Conclusion

Who would have thought that such beautiful physics was contained in a simple pencil? Graphene is one of the hottest new materials in physics today. Although it is still too early to predict its future, the purity of the atomic monolayer is such that beautiful fundamental physics will continue to be observed. Its commercial aspect will only be made possible by the development of large scale processes for graphene wafers or sheets, Nevertheless beautiful fundamental physics has been and will be studied thanks to this discovery, and a high predicted specimen surface area, together with the exotic transport phenomena it exhibits make it a serious candidate for numerous future studies. It is difficult to predict exactly the future of this material.

For a few years, graphene research has exploded in some physical application fields, particularly, in flexible electronics. However, graphene research into bioengineering applications was relatively moderate until recently. As the more fascinating properties of graphene materials are revealed, and more interdisciplinary research

efforts are attempted worldwide, more and more possibilities for graphene as a biomaterial are now being actively discovered. Thus, in this project work, comprehensively surveyed recent experimental work related to tissue engineering and tissue regenerative medicine utilizing graphene or graphene derivatives. The exceptional properties of graphenes are now being incorporated into many functional biological materials. Cell scaffolds, which modulate cell growth, sitting patterns, and differentiation, are just one example of graphene utilization towards better tissue regenerative medicine. Furthermore, functional graphenes form biocompatible complexes with various drugs that would otherwise be extremely difficult to deliver in physiological solutions. These complexes can be designed to deliver drugs to any desired site within bodily organs and tissues, because of both their safety and functionality within living biological. In addition, graphene, as a soft electronic material, could find distinct roles in neural interface engineering. The examples introduced in the review all corroborate the bright future of graphene for applications in biological tissue engineering.

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