Biological and Environmental Impacts of Disulfide-BasedPolymericNanomaterials: A ComprehensiveReview

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Abstract

Nanomaterials have become a transformative field in materials science and engineering, revolutionizing diverse industries and applications. Among these, disulfide-based polymeric nanomaterials have gained attention for their versatility and environmental relevance. This comprehensive review explores the biological and environmental impacts of disulfide-based polymeric nanomaterials within the broader context of nanotechnology. The significance of nanomaterials in various applications is outlined, showcasing their impact on electronics, medicine, environmental remediation, and energy production. Specifically, disulfide-based polymeric nanomaterials are introduced, emphasizing their importance in nanotechnology.The review objectives include summarizing the current state of knowledge on the synthesis and characterization of disulfide-based polymeric nanomaterials, investigating their biological implications, examining their environmental impacts, and evaluating safety and toxicity. Potential strategies and recommendations for the responsible and sustainable use of these nanomaterials are outlined. The synthetic methods of disulfide-based polymeric nanomaterials are explored, including polymerization of disulfide monomers, thiol-disulfide exchange, oxidation of thiol-containing polymers, nanoparticle encapsulation, and self-assembly. Each method offers distinct advantages for tailoring the properties of these materials. The properties of disulfide-based polymeric nanomaterials, such as redox responsiveness, biodgradability, tailorability, and biocompatibility, are discussed. The impact of synthetic strategies on these properties is emphasized, highlighting the importance of choosing appropriate methods for specific applications.

1. Introduction

Nanomaterials have emerged as a transformative field in the realm of materials science and engineering, revolutionizing numerous applicationsandindustries. With theiruniqueproperties at thenanoscale, these materials have found applications in fields ranging from electronics and medicine to environmentalremediation and energy production [1]. The unparalleled success and potential of nanomaterials have spurred extensive research into their synthesis, characterization, and applications. Within this vast landscape of nanomaterials, disulfide-basedpolymericnanomaterials have attracted increasingattention due to theirversatility and environmentalrelevance[2].

This comprehensive review seeks to shed light on the biological and environmental impacts of disulfide-basedpolymericnanomaterials. Before looking into theintricacies of this subject, it is essential to provide a briefoverview of theoverarchingsignificance of nanomaterials in various applications. Following this, we will introduce the readers to thespecificrealm of disulfide-basedpolymericnanomaterials and elucidatetheirimportance in the broader context of nanotechnology. Finally, we will out linethepurpose of this review, which is to synthesizeexistingknowledge and evaluatethe biological as well astheenvironmentalconsequences of theseuniquenanomaterials.

1.1 The Significance of Nanomaterials in Various Applications

Nanomaterials, typically defined as materials with at least one dimension in thenanoscale range (1-100 nanometers), have demonstratedremarkableproperties and capabilities that distinguish them from their bulk counter parts [3]. These unique characteristics stem from their high surface area-to-volume ratio, quantum size effects, and increased reactivity, making them invaluable in various applications [4]. Some of the key domains where nanomaterials have made substantial contributions include:

Medicine and Healthcare: Nanomaterials have opened new frontiers in drug delivery, diagnostics, and therapeutics[5]. Nanoparticles can be engineered to target specific cells or tissues, improving drug delivery efficiency and reducingsideeffects. Additionally, nanoscale imaging agents have enabledearly disease detection and precise diagnostics.

EnergyStorage and Conversion: Nanomaterialshave played a crucial role in advancing renewableenergytechnologies. Nanomaterial-based catalysts have enhancedtheefficiency of fuel cells and electrolyzers, whilenanocomposites have improved theperformance of lithium-ion batteries and solar cells[6].

EnvironmentalRemediation: Nanomaterials have shown promise in environmentalcleanup and pollution control. For instance, nanoparticles can efficiently remove contaminants from water and air, while nanoscalephotocatalysts can degrade pollutants in wastewater and air pollutants[7].

Materials Science and Engineering: Nanomaterials have led to thedevelopment of advanced materials with enhancedmechanical, thermal, and electricalproperties. For example, carbon nanotubes and graphene have providedexceptional strength, conductivity, and heat transfer capabilities to various materials[8].

1.2 Disulfide-BasedPolymericNanomaterials and TheirImportance

Within the diverse field of nanomaterials, disulfide-basedpolymericnanomaterialsrepresent a class of materials that have gained prominence due to theirspecificcharacteristics and applications (Lipoic acid-based poly(disulfide)s). These nanomaterialsare primarily composed of disulfide (S-S) bonds in theirstructure, which play a pivotal role in theirproperties and behavior. Disulfide-basedpolymers can be synthesized with differentarchitectures, such as linear or branched, and can be functionalized to tailor theirproperties for specific applications [910]. The importance of disulfide-basedpolymericnanomaterials can be attributed to several key factor (small size, high surface area-to-volume ratio, and ability to absorb and scatter light in the visible and near-infrared range). Disulfide-basedpolymericnanomaterialsare often biocompatible, making themsuitable for use in biomedical applications (drug delivery). Their biocompatibility arises from thepresence of disulfide bonds, which are found in many biological molecules and their compatibility with biological systems. These nanomaterials have been extensivelyexplored as carriers for drug delivery [2]. Disulfide-basedpolymericnanomaterialsexhibit redox responsiveness due to thepresence of disulfide bonds. This property is particularly valuable in drug delivery and bioimaging applications, as it enablesthe release of cargo in response to changes in the redox environment[11].The redoxsensitivity of disulfide-basedpolymericnanomaterialsextends to theirpotentialenvironmental applications. They can be used for thecontrolled release of remediationagents in response to specificenvironmental conditions. These nanomaterials can be engineered to possess a wide range of properties, such as tunablesize, surfacecharge, and surfacefunctionalization, making themsuitable for diverse applications in nanomedicine, nanotechnology, and environmentalscience[12].

The purpose of this comprehensive review is to provide a detailed examination of the biological and environmental impacts of disulfide-basedpolymericnanomaterials. In recentyears, thesenanomaterials have shown significant promise in various applications, particularly in thefields of drug delivery, diagnostics, and environmentalremediation. However, as with any emerging technology, it is essential to evaluatetheirpotentialconsequences on biological systems and theenvironment[13]. This review aims to fulfill the following objectives. Summarizethecurrent state of knowledge on the synthesis and characterization of disulfide-basedpolymericnanomaterials. Investigatethe biological implications of using thesenanomaterials, including theirinteractions with cells, tissues, and the human body. Examinetheenvironmental impacts of disulfide-basedpolymericnanomaterials, particularly in thecontext of their applications in pollution control and environmentalremediation. Evaluate the safety and toxicity of thesenanomaterials, both in vitro and in vivo, to understand their potential risks [14]. Highlight potentialstrategies and recommendations for theresponsible and sustainable use of disulfide-basedpolymericnanomaterials in various applications. By addressing theseobjectives, this review aims to provide a comprehensiveunderstanding of the biological and environmentalaspects of disulfide-basedpolymericnanomaterials, offering insights for researchers, policy makers, and practitioners working in nanotechnology, biomedicine, and environmentalscience. Ultimately, this knowledge will contribute to the informed and ethical utilization of thesenanomaterials in ways that benefit societywhile minimizing potential risks.

2 Synthesis of Disulfide-BasedPolymericNanomaterials

Disulfide-basedpolymericnanomaterials have gained substantial attention due to theiruniqueproperties and diverse applications. The synthesis of these materials is a crucial step in harnessingtheirpotential. In this discussion, we will explorethemethods for the synthesis of disulfide-basedpolymericnanomaterials, theirproperties, and the impact of synthetic strategies on theircharacteristics and applications.

2.1 Methods for Synthesis

The synthesis of disulfide-basedpolymericnanomaterials is a versatile and customizableprocess. Researchers have developed various techniques to create these materials, each offering distinct advantages and tailored properties. Some common methods for synthesizing disulfide-basedpolymericnanomaterials include:

2.1.1 Polymerization of DisulfideMonomers

One of the most fundamental approaches is thepolymerization of disulfide-containingmonomers. These monomers can be designed to possessdisulfidelinkages within theirmolecularstructure, allowing for straight forward polymerizationprocesses (figure 1). Radical polymerizationtechniques, such as free radical polymerization, are commonly used to produce disulfide-basedpolymers. These techniquesinitiatepolymerization by creating free radicals that react with disulfidemonomers to form polymer chains. The resultingpolymers can vary in molecularweight and architecture based on the choice of monomers and reaction conditions [15].

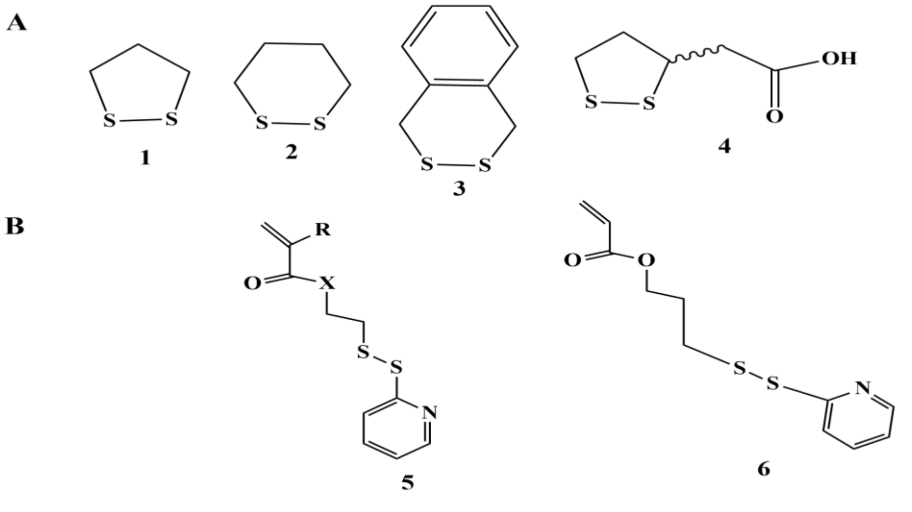


Figure 1(A) Cyclic disulfide monomers used for thermal- and photo-induced radical ring-opening polymerizations, and (B) monomers containing pyridyl disulfide groups.

2.1.2 Disulfide Bond Formation via Thiol-DisulfideExchange

The thiol-disulfideexchange reactions offer an alternative route for disulfide-basedpolymericnanomaterial synthesis. This methodinvolvesthe reaction of thiol (SH) groups with disulfide (S-S) bonds to form new disulfidelinkages (figure 2). Such reactions can occur under mild conditions and are particularly useful for modifying existingpolymers to introduce disulfide functionality. By controlling thestoichiometry and reactivity of thiol groups, researchers can tailor theproperties of theresulting materials, including crosslinkingdensity and mechanicalstrength[1617].

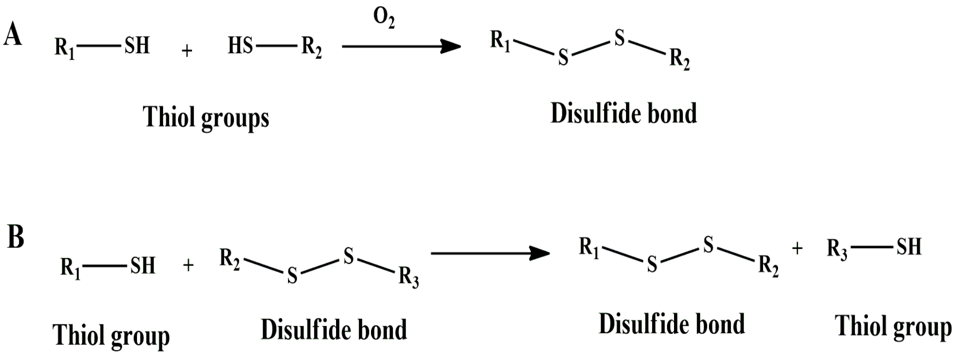
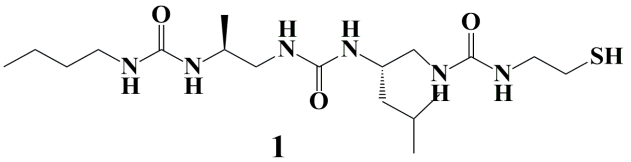


Figure 2 Thiol Chemistry: (A) Disulfide formation through oxidation reaction, and (B) disulfide-exchange reaction.

2.1.3 Oxidation of Thiol-Containing Polymers

Anotherstrategy for synthesizing disulfide-basedpolymericnanomaterialsinvolvesthe oxidation of thiol-containing polymers (figure 3). This process typically involvesthe use of an oxidizing agent, such as hydrogenperoxide or iodine, to convert thiol groups into disulfide bonds. The resulting materials are often characterized by disulfidelinkages within thepolymerbackbone, enhancingtheir redox responsiveness. This method is useful for producing disulfide-basednanomaterials with controlledchemicalstructures and functionalities[18].



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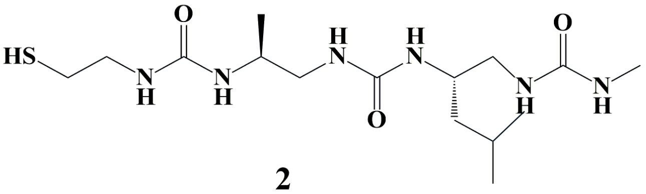

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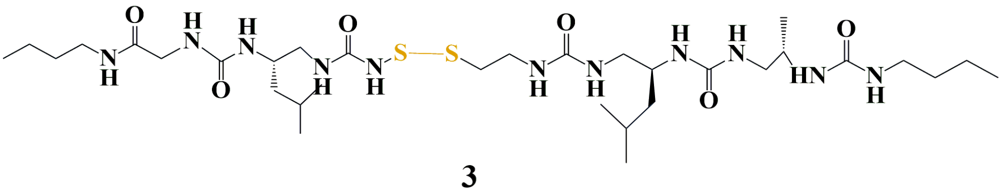

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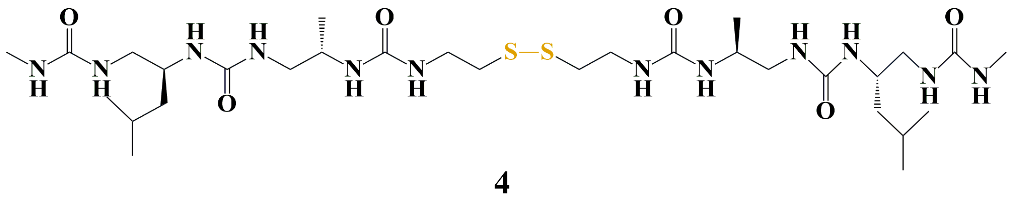

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Figure 3 Thiol substrates (compounds 1 and 2) and corresponding disulfide products (compounds 3 and 4).

2.1.4 Nanoparticle Encapsulation:

In some cases, disulfide-basedpolymericnanomaterialsaresynthesized by encapsulating or grafting disulfide-containingpolymers onto existingnanoparticles (figure 4). Nanoparticles can serve as carriers for disulfide-basedmaterials, enhancingtheir stability and facilitating applications such as drug delivery. The encapsulationprocessinvolvesthepreparation of disulfide-basedpolymers, followed by the association with nanoparticles through surfaceinteractions, covalent bonding, or electrostatic attraction [19].

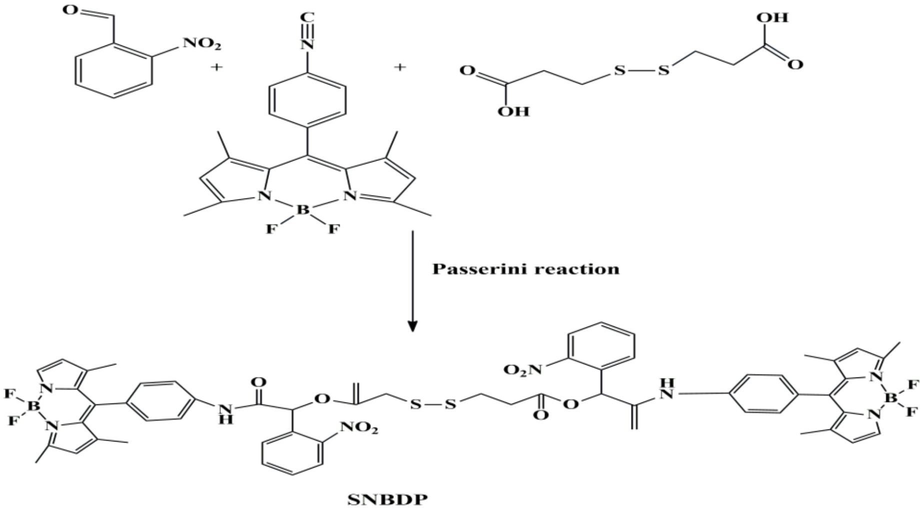

Figure 4 Synthesis of the SNBDP via multi-component Passerini reaction.

2.1.5 Self-Assembly and Micelles

Disulfide-basedpolymericnanomaterials can also be synthesized via self-assemblyprocesses. Amphiphilic block copolymers containing disulfide groups can self-assemble into micelles or othernanostructures in specificsolvents (figure 5). The resulting micelles can encapsulate hydrophobic drugs or payloads, making themsuitable for drug delivery applications. The disulfide bonds in these materials enableredox-responsive drug release upon exposure to reducingenvironments, such as those found intracellularly[20].

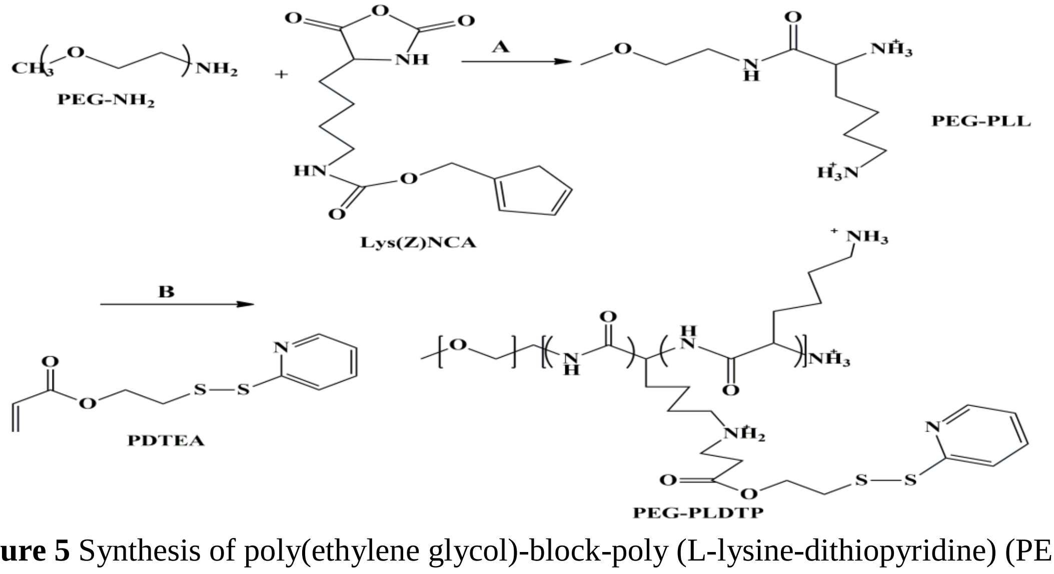

Figure 5 Synthesis of poly(ethylene glycol)-block-poly (L-lysine-dithiopyridine) (PEG-PLDTP). (A) Ring-opening polymerization of PEG-NH2 with the N-carboxyanhydride (NCA) of Cbz-protected lysine (Lys(Z)-NCA) to generate PEG-poly (L-lysine) (PEG-PLL). (B) Graftin.

3 Properties of Disulfide-BasedPolymericNanomaterials

Disulfide-basedpolymericnanomaterialsexhibitseveral key properties that makethem highly attractive for a wide range of applications. These propertiesareclosely tied to theirchemicalstructure, which is characterized by disulfide (S-S) bonds.

3.1 Redox Responsiveness

The most prominentfeature of disulfide-basedpolymericnanomaterials is their redox responsiveness. The disulfide bonds within thepolymerbackbone can be cleaved in response to specific redox conditions, such as high intracellularglutathione levels. This propertyenablescontrolled drug release in targeted delivery systems, making themsuitable for anticancertherapies, where tumor cells often exhibit higher glutathioneconcentrations than healthycells[21].

3.2 Biodegradability

Due to theirredox-sensitivenature, disulfide-basedpolymericnanomaterialsareinherentlybiodegradable. Whenexposed to reducing conditions, such as those found within cells or thehuman body, thedisulfide bonds break, leading to the degradation of thepolymer. This propertyminimizesthe accumulation of non-biodegradable materials in biological systems and reducespotential toxicity concerns[22].

3.3 TailorableProperties

The synthesis of disulfide-basedpolymericnanomaterials can be tailored to achievespecificproperties, including molecularweight, crosslinkingdensity, and functional groups. By choosing appropriatemonomers and controlling reaction conditions, researchers can customizethese materials to suit theirintended applications. This versatility allows for thedevelopment of materials with propertiesoptimized for drug delivery, environmentalremediation, or otherpurposes[23].

3.4 Biocompatibility

Many disulfide-basedpolymericnanomaterialsarebiocompatible, making themsuitable for use in medical and biological applications. Their biocompatibility is partly attributed to thepresence of disulfide bonds in many biological molecules. This featureensures minimal cytotoxicity and immunogenicity, enhancingtheir suitability for drug delivery and diagnostic tools[24].

4 Impact of Synthetic Strategies on disulfide-basedpolymericnanomaterials

The choice of synthetic method plays a significant role in determiningtheproperties of disulfide-basedpolymericnanomaterials. Different synthetic approaches can influencethe material's redox responsiveness, biodegradability, and overallperformance in specific applications. Researchers must carefully considerthemethod that aligns with theirintended goals.

For instance, thepolymerization of disulfidemonomers can provide high control overmolecularweight and architecture, but thechoice of monomers and polymerization conditions is critical. Thiol-disulfideexchange reactions offer a route to introducedisulfidelinkages into existingpolymers, offering a convenient approach to modify materials with desired properties[15]. Oxidation of thiol-containing polymers is a precise method for generating well-defined disulfide-based materials.

Encapsulation onto nanoparticles or self-assembly into micelles offers strategies to enhance stability and enable drug delivery [25]. The choice of synthesis should align with thespecificrequirements of theintended application, allowing for the customization of disulfide-basedpolymericnanomaterials to meet thedemands of various fields, including biomedicine, nanotechnology, and environmentalscience[26]. These versatile materials continue to evolve, opening new possibilities for innovative solutions in both research and practical applications.

5 Structural Characteristics of Disulfide-BasedPolymericNanomaterials

Disulfide-basedpolymericnanomaterials have garnered significant attention in recentyears due to theirunique structural characteristics and properties. These nanomaterialsareengineered with disulfide (S-S) bonds in theirstructure, which bestow them with distinctivefeatures that makethemvaluable in various applications. In this section, we will look into the structural characteristics and properties of disulfide-basedpolymericnanomaterials to gain a betterunderstanding of theirversatilenature and capabilities.

Disulfide-basedpolymericnanomaterialsare defined by thepresence of disulfide bonds within theirstructures. These bonds arecovalentlinkages formed between two sulfur atoms, which can vary in thearrangement and bonding patterns. The disulfide bond, S-S, is also known as a disulfidelinkage, and it plays a fundamental role in the structural stability and properties of thesenanomaterials[27]. The polymericcomponent of disulfide-basednanomaterials typically comprises a polymerbackbone. This polymer can be of various types, such as polyethylene glycol (PEG), poly(lactic-co-glycolic acid) (PLGA), or others. The choice of thepolymerbackboneinfluencesthenanomaterial's solubility, biocompatibility, and degradation kinetics [28]. These materials can be synthesized in a range of nanostructures, including nanoparticles, nanogels, nanomicelles, and nanocapsules, to name a few. The specificnanostructure can betailored to optimizethenanomaterial'sintended application. For instance, nanoparticlesaresuitable for drug delivery, whilenanogels can serve as carriers for controlled release [29]. Thesurface of disulfide-basedpolymericnanomaterials can be functionalized with various chemical moieties. This allows for theattachment of targeting ligands, imaging agents, or other functional groups, enhancingtheirspecificity and versatility for different applications.

6 Biocompatibility and Toxicity Assessment of Disulfide-BasedPolymericNanomaterials

Biocompatibility is a critical considerationwhen developing and utilizing nanomaterials, especially in biomedical applications. Understanding how nanomaterialsinteract with living organisms and theirpotential toxic effects is essential for ensuringthesafety and efficacy of thesematerials [30]. This discussion focuses on thestudies that have assessedthe biocompatibility of disulfide-basedpolymericnanomaterials, shedding light on thepotential benefits and concernsassociated with their use in various applications. Disulfide-basedpolymericnanomaterials have gained considerableattention due to theiruniqueproperties, such as redox responsiveness, biocompatibility, and versatility.

These characteristicsmakethem promising candidates for drug delivery systems, diagnostic agents, and therapeutics[31]. However, before thesenanomaterials can be widely adopted in biomedicalsettings, it is crucial to evaluatetheir biocompatibility and potential toxicity.

6.1 Biocompatibility Assessment of Disulfide-BasedPolymericNanomaterials

Severalstudies have been conducted to assessthe biocompatibility of disulfide-basedpolymericnanomaterials, focusing on theirinteractions with cells, tissues, and living organisms. These assessments aim to determinewhetherthesenanomaterialsaresafe for use in biomedical applications, including drug delivery and diagnostics.

Many biocompatibility assessments begin with in vitro experiments, wheredisulfide-basedpolymericnanomaterialsareexposed to different cell types to evaluatetheir cytotoxicity and compatibility. These studies typically use cell linesrepresentative of targettissues to assess cell viability, proliferation, and any potentialadverseeffects. In numerousstudies, disulfide-basedpolymericnanomaterials have demonstrated high cell viability, indicating their biocompatibility [32]. For example, a study exposed human mesenchymalstemcells to disulfide-basedpolymericnanoparticles, revealing no significant cytotoxicity and even promoting cell proliferation. Hemolysis assays areused to assessthepotential for red blood cell damage. Disulfide-basedpolymericnanomaterials have been found to exhibit low hemolytic activity in thesetests, further confirming their biocompatibility [33]. After successful in vitro assessments, researchers proceed to in vivo studies, which involvethe administration of disulfide-basedpolymericnanomaterials to living organisms, typically rodents or othermodel organisms. These studiesprovide insights into thenanomaterials' compatibility with complex biological systems. In vivo studies have shown that disulfide-basedpolymericnanomaterials can be administered to animals without causing significant adverseeffects. These nanomaterials have been used in drug delivery systems with encouragingresults[34]. For example, disulfide-basednanoparticles for the delivery of chemotherapeuticagents, demonstratingtheireffectiveness in treatingtumor-bearing mice with minimal toxicity. Understanding how disulfide-basedpolymericnanomaterialsaredistributed and eliminated from the body is crucial. Some studies have showed that these materials tend to accumulate in the liver and spleen, wheretheyareeventuallyclearedovertime[35]. This information helps in designing effective drug delivery strategies and minimizing potential long-term toxicity.

Biocompatibility assessments also considerthe immunological response to disulfide-basedpolymericnanomaterials. Understanding how theimmunesysteminteracts with these materials is essential for predictingpotentialadverse reactions. Studies have shown that disulfide-basedpolymericnanomaterials can exhibitimmunomodulatoryeffects. For instance, they can stimulatethe production of specificcytokines that enhanceimmuneresponses[36]. While this property can bebeneficial for some applications, it may also raiseconcerns about immune-relatedsideeffects. To fully assess biocompatibility, long-term studiesareessential. These investigationsexaminethecumulativeeffects of disulfide-basedpolymericnanomaterialexposureoverextendedperiods. Long-term studies can helpidentifypotentialissues that may not be evident in short-term assessments.

6.2 Toxicity Assessment of Disulfide-BasedPolymericNanomaterials

In addition to biocompatibility, thepotential toxicity of disulfide-basedpolymericnonmaterial must be thoroughly investigated. Toxicity assessments aim to identify any adverseeffects that may result from exposure to thesenonmaterials. Acute toxicity assessmentsdeterminetheimmediate harmful effects of disulfide-basedpolymericnanomaterials. This typically involvesevaluatingtheir impact on vital organs, such as the liver, kidneys, and lungs, after short-term exposure[37]. Studies have demonstrated that disulfide-basedpolymericnanomaterials do not induce significant organ damage in short-term exposureexperiments. This suggests a low risk of acute toxicity. Chronic toxicity assessmentsexplorethe long-term effects of disulfide-basedpolymericnanomaterialexposure. These studiesareessential for understandingthepotential risks associated with continuous or repeated use [38]. Chronic exposurestudies have shown that disulfide-basedpolymericnanomaterials can accumulate in certain organs, such as the liver, overtime. While accumulation itself may not be toxic, it necessitatesfurtherinvestigation to determine its long-term implications. Genotoxicity and mutagenicityassessmentsinvestigatewhetherdisulfide-basedpolymericnanomaterials can causedamage to DNA or induce mutations in cells[39]. Most studies have not reported significant genotoxiceffects from disulfide-basedpolymericnanomaterials. This suggests a low risk of genetic damage. Toxicity assessments should also considertheenvironmental impact of disulfide-basedpolymericnanomaterialswhentheyare released into ecosystems. This includesevaluatingtheireffects on aquatic life, soil health, and potential bioaccumulation (figure 6) [40]. Some studies have assessedthe impact of disulfide-basedpolymericnanomaterials on aquatic organisms and have found that, depending on theconcentration, these materials can have varying effects on aquatic life[41].

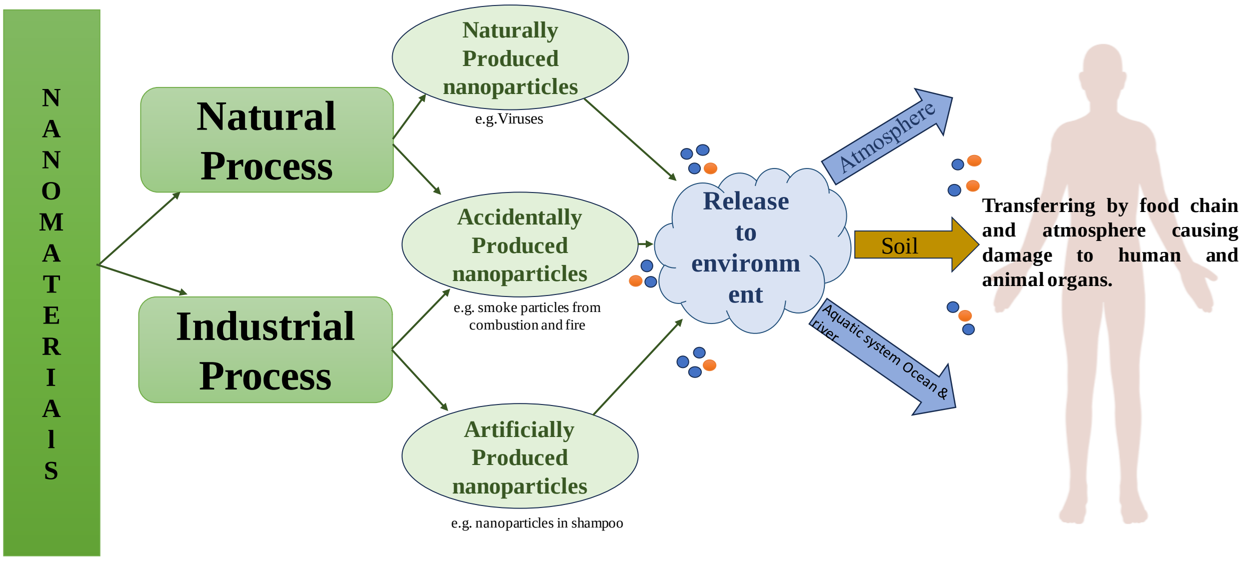

Figure 6 Effects of nanomaterials when released in environment.

The assessment of biocompatibility and toxicity of disulfide-basedpolymericnanomaterials is crucial to theirsafe and effective utilization in various applications. The studies discussed above reveal severalkey findings and considerations as discussed below.

6.2.1 Biocompatibility

Disulfide-basedpolymericnanomaterials generally exhibit good biocompatibility, as demonstrated by high cell viability in in vitro studies and limited adverseeffects in animal models. Their biocompatibility makesthem promising candidates for drug delivery, wherethey can effectively transport therapeuticagents without significant harm to cells or tissues[42].

6.2.2 Redox Responsiveness

The redoxsensitivity of disulfide-basedpolymericnanomaterials can be advantageous in biomedical applications. The ability to release cargo in response to specificintracellular conditions, such as elevated glutathione levels, is a valuablefeature for targeted drug delivery [43].

6.2.3 Immunomodulation

Some disulfide-basedpolymericnanomaterialsexhibitimmunomodulatoryeffects. While this property can enhanceimmuneresponses and be beneficial for certain applications and it may also raiseconcerns about potentialimmune-relatedsideeffects that need furtherinvestigation[44].

6.2.4 Toxicity

Acute toxicity assessmentssuggest low risk, with no significant organ damageobserved in short-term exposurestudies. However, long-term and chronic toxicity assessmentsindicatethepotential for tissue accumulation, which warrants furtherinvestigation to determine its long-term effects[45].

The biocompatibility and toxicity assessments of disulfide-basedpolymericnanomaterials have yielded promising results, particularly in thecontext of drug delivery and otherbiomedical applications. However, the long-term effects of tissue accumulation and thepotential for immune modulation requirefurtherinvestigation. Additionally, responsiblemanagement and disposal practicesareessential to mitigate any potentialenvironmental impact [30]. As research in this field continues to advance, a comprehensiveunderstanding of the benefits and risks associated with thesenanomaterials will aid in theirsafe and effective utilization in various applications, ultimatelybenefitinghealthcare, environmentalremediation, and beyond.

6.3 Examination of Potential Toxicological Concerns and Methods for Toxicity Assessment

In therealm of nanomaterials, theassessment of potential toxicological concerns is a paramount consideration. As nanotechnologycontinues to advance, researchers and regulatorybodies must thoroughly investigate and understandthepotential risks associated with nanomaterialexposure. This examinationinvolvesidentifyingthemechanisms of toxicity, evaluatingthepotentialadverseeffects on biological systems, and developing robust methods for toxicity assessment[46]. In this discussion, we look into the critical aspects of potential toxicological concernsassociated with nanomaterials and explorethemethodsemployed to assesstheir toxicity. Nanomaterials, including disulfide-basedpolymericnanomaterialspossessuniqueproperties at thenanoscale that can giverise to potential toxicological concerns.Theseconcernsarise from various characteristics and interactions, including size, surfaceproperties, and reactivity [29]. One of the most notablefeatures of nanomaterials is theirsize, typically falling in the range of 1-100 nanometers. This small size can lead to novel biological interactions. For instance, nanoparticles in this sizerange may exhibitenhancedcellular up take, leading to potential cytotoxicity [47]. Furthermore, nanoparticles can penetratecellularbarriers, including the blood-brain barrier, raising concerns about neurotoxicity. The surfaceproperties of nanomaterialsare of critical importance in determiningtheir toxicity. Functionalization and surface modifications can influencethenanomaterial'sinteractions with biological systems. In somecases, functionalization may enhancebiocompatibility;while in others may lead to unforeseen toxic effects[48]. Moreover, thecharge and ligands on thesurface of nanomaterials can alter theirbehavior and influence toxicity. Certainnanomaterials, particularly those with uniqueredox-activepropertieslikedisulfide-basedpolymericnanomaterials, can generate reactiveoxygenspecies (ROS) or reactive sulfur species (RSS) underspecific conditions. These reactivespecies can induceoxidativestress, damagebiomolecules, and trigger inflammatory responses, which areassociated with various adversehealtheffects, including carcinogenesis and organ damage[49]. Nanomaterials may agglomerate or aggregate in biological fluids, altering theirsize, surfacearea, and reactivity. Such changes can influencetheirbehavior within the body and affecttheir toxicity. Agglomeratednanoparticles may have different biological interactions and distribution patterns than individual nanoparticles, leading to varying toxicological outcomes[50]. Anotherconcern is the long-term persistence of nanomaterials within the body or theenvironment. Some nanoparticles can accumulate in tissues or organs, potentially causing chronic toxicity. Additionally, the fate of nanomaterials in theenvironment, including theirpotential to bioaccumulate in aquatic ecosystems, raisesecologicalconcerns.

6.4 Methods for Toxicity Assessment

To assessthepotential toxicity of nanomaterials, a range of methods and experimental approaches have been developed. These methodsare designed to examine various aspects of nanomaterialinteractions with biological systems, such as cytotoxicity, genotoxicity, and immunotoxicity. Some commonly used methods for toxicity assessmentinclude:

6.4.1 In Vitro Studies

In vitro studiesinvolve using cell cultures to assessthe toxicity of nanomaterials. These studiesprovide insights into cellularresponses to nanomaterialexposure. These testsevaluate cell viability and assessthepotential for nanomaterials to cause cell death or inhibit cell growth [51]. Genotoxicitystudiesassessthepotential of nanomaterials to damage DNA and induce mutations in cells. These assays investigatethe ability of nanomaterials to trigger inflammation in cells, often by measuringthe release of pro-inflammatory cytokines[52].

6.4.2 In Vivo Studies

In vivo studiesinvolveexposing animals to nanomaterials to evaluatetheireffects on living organisms. These studiesprovide insights into systemic and organ-specific toxicity. These studiesassesstheimmediate toxic effects of nanomaterialexposure, including symptoms, organ damage, and mortality [53]. These investigationsassessthe long-term effects of nanomaterialexposure, including potentialcarcinogenicity, organ toxicity, and reproductive toxicity. These studies track the distribution, metabolism, and elimination of nanomaterials in the body to understandtheirlong-termfate[54]. Computational modeling and predictive toxicology tools have become increasingly important in assessingnanomaterial toxicity. These approaches use algorithms and simulations to predict potential toxic effects based on nanomaterialproperties, structure-activityrelationships, and known mechanisms of toxicity [55]. They offer valuable insights early in thedevelopment of nanomaterials, helping to prioritizethesafestcandidates for further testing. Assessingtheenvironmental impact of nanomaterials is crucial. Ecotoxicitystudiesinvolveexposing aquatic organisms or soil-dwelling organisms to nanomaterials to evaluatetheireffects on ecosystems. These studiesexamine parameters such as survival, reproduction, and behavioralchanges in exposed organisms [56].

6.4.3 Regulatory Framework and Risk Assessment

The assessment of nanomaterial toxicity is tightly integrated with regulatoryframeworks and risk assessmentprocedures. Differentregions and countries have establishedguidelines for thesafe use of nanomaterials in various applications, including medicine and consumer products. Regulatoryagencies, such as the U.S. Food and Drug Administration (FDA) and theEuropeanMedicinesAgency (EMA), requireextensive toxicity data for nanomaterials before approving their use in pharmaceuticals or medical devices [57]. Risk assessmentencompasses hazard identification, exposureassessment, and risk characterization. By combining toxicity data from various studies with information on exposure levels and pathways, risk assessors can estimatethepotential risks of nanomaterials to human health and theenvironment. This process informs regulatorydecisions and helpsestablishsafeexposure limits.

6.4.4 Strategies for Mitigating Toxicity

In theface of potential toxicological concernsassociated with nanomaterials, researchers and manufacturersareactively developing strategies to mitigate toxicity. These strategies aim to design nanomaterials that have reducedadverseeffectswhileretainingtheirbeneficialproperties[58]. Some approaches includesurface modifications, such as functionalization with biocompatible ligands, can enhancethe biocompatibility of nanomaterials. This reducestheirpotential to cause toxicity by promoting interactions that areless harmful to biological systems[59]. Encapsulating nanomaterials within biocompatible coatings or matrices can preventdirect contact with cells and tissues, minimizing potential toxic effects. This approach is commonly used in drug delivery systems to protect payloads and control their release. Utilizing theuniqueproperties of nanomaterials for targeted drug delivery can minimizeoff-target toxicity [59]. By functionalizingnanomaterials to selectivelyinteract with specificcells or tissues, therapeutic payloads can be delivered more precisely. Engineeringnanomaterials to enablecontrolled release of cargo in response to specific stimuli, such as changes in pH or redox conditions, can reducethe risk of overexposure and associated toxicity [60]. Developing nanomaterials that arebiodegradableensures that theybreak down into harmless byproducts after fulfilling theirintended function. This approach minimizes long-term persistence and associated toxicity. The assessment of potential toxicological concerns and thedevelopment of effectivemethods for toxicity assessmentare crucial components of responsiblenanomaterial research and application As the field of nanotechnologycontinues to expand, it is imperative to evaluatethe risks associated with theuniqueproperties and interactions of nanomaterials. This involves not only identifyingpotential hazards but also developing strategies to mitigate toxicity and protect human health and theenvironment[61]. Whiledisulfide-basedpolymericnanomaterials and othernanomaterials offer promising opportunities in various domains, including medicine, environmentalremediation, and materials science, understanding and addressingtheirpotential toxicological concerns remain paramount [31]. Ongoing research, regulatoryoversight, and collaborativeeffortsbetweenscientists, industry, and regulatoryagencies will ensure that the benefits of nanotechnology can be harnessedsafely and responsiblywhile minimizing potential risks.

7 Interactions with Biological Systems: How Disulfide-BasedPolymericNanomaterialsInteract with Cells and Tissue

Disulfide-basedpolymericnanomaterials have earnered increasingattention in the field of nanomedicine due to theiruniqueproperties and versatile applications. Understanding, how thesenanomaterialsinteract with biological systems, particularly cells and tissues, is pivotal in harnessingtheir full potential for various biomedical applications. In this section, we will through lightontheintricate world of thesenanomaterials and exploretheirinteractions with biological entities[22]. One of the most crucial aspects of disulfide-basedpolymericnanomaterials' interaction with biological systems is their ability to be internalized by cells. The cellular up take of thesenanomaterialsdepends on multiple factors, including theirsize, shape, surfacecharge, and functionalization. Theirnanoscaledimensionsenableefficientcellular up take, as they can exploit various endocytic pathways [62]. Severalstudies have shown that thesenanomaterials can entercells via receptor-mediatedendocytosis, clathrin-mediatedendocytosis, caveolae-mediatedendocytosis, or macropinocytosis, depending on thespecificproperties of thenanomaterial and thetarget cell type (figure 7). Onceinternalized, disulfide-basedpolymericnanomaterials can release their cargo which is particularly advantageous for drug delivery applications, as it allows for controlled and targeted release of therapeuticagents within thecells[21].

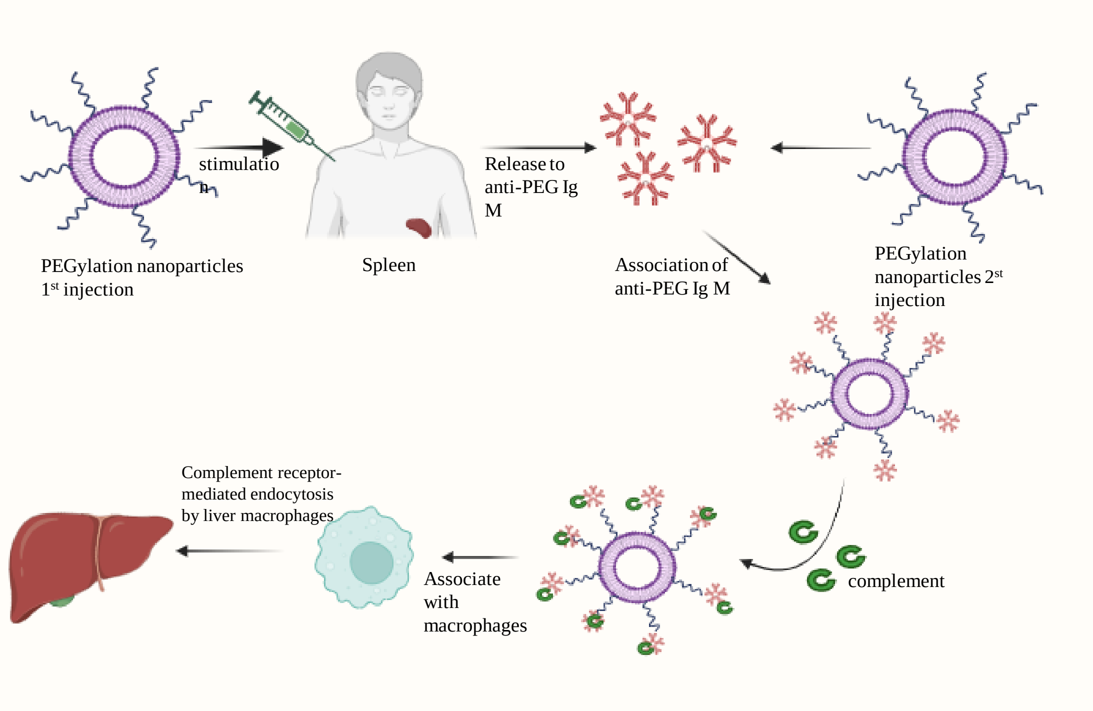

Figure 7: Disulfide-basedpolymericnanomaterialsinteract with cells and tissue.

Disulfide-basedpolymericnanomaterials may also interact with various biomolecules within biological systems. The presence of disulfide bonds in thesenanomaterialsenablesthem to participate in redox reactions, responding to theuniqueoxidativeenvironment within cells. This redox responsiveness is particularly valuable in drug delivery applications, wherethedisulfidelinkages can be cleaved in response to elevated intracellularglutathione levels [63]. This specificinteraction leads to the release of cargo molecules, improving theefficiency and precision of drug delivery. Furthermore, thesurfacechemistry of thesenanomaterials plays a crucial role in determiningtheirinteractions with biomolecules. By functionalizingthenanomaterialsurfaces with specific ligands or targeting moieties, researchers can enhancetheir ability to selectivelyinteract with biomolecules such as receptors on cellsurfaces[57]. This targetedinteraction is instrumental in improving theefficiency and specificity of drug delivery, diagnostic agents, and thenanosystems. The biodistribution of disulfide-basedpolymericnanomaterials within biological systems is influenced by theirsize, shape, and surfaceproperties. Typically, nanomaterials with smaller sizes have an advantage in terms of tissuepenetration, which allows them to reachdeep-seatedtargets. Theirsurfacecharge and functionalization can also impact their distribution in vivo, affectingtheir accumulation in specifictissues or organs [22]. In some applications, researchers exploitthesepropertiesto enhancetissue-specifictargeting. By engineeringdisulfide-basedpolymericnanomaterials with ligands that bind to receptors or antigensoverexpressed on certain cell types or tissues, they can achievetargeted delivery and improved therapeuticoutcomes. This targeted approach reducesoff-targeteffects, minimizing the impact on healthytissues and enhancingtheeffectiveness of treatment[64]. Evaluating the toxicity and biocompatibility of disulfide-basedpolymericnanomaterials is essential to ensuretheirsafe use in biological systems. Whilethesenanomaterials offer many advantages in terms of drug delivery and biomedical applications, potentialadverseeffects must be carefully considered[30]. Toxicity studiesinvolveassessingthe impact of thesenanomaterials on cellular viability, proliferation, and the induction of inflammatory responses. The good news is that many disulfide-basedpolymericnanomaterialsexhibit a high degree of biocompatibility, especiallywhen designed for controlled drug release applications [65]. The presence of disulfide bonds, which are naturally found in biological systems, contributes to their biocompatibility. Additionally, their ability to respond to theintracellular redox environmentprovides a level of safety, as the cargo release is contingent on specific conditions. Nevertheless, it is crucial to note that the toxicity of thesenanomaterials may vary depending on factors likesize, concentration, and surface modifications. Comprehensive in vitro and in vivo studiesareessential to assessthesafety of disulfide-basedpolymericnanomaterials under various conditions and applications. The interaction of disulfide-basedpolymericnanomaterials with theimmunesystem is another important aspect to consider[66]. Surfacefunctionalization of thesenanomaterials can be strategically designed to minimize immunological recognition, preventingundesirableimmuneresponses. PEGylation (polyethylene glycol coating) is a common approach to renderthenanomaterialsurface, reducinginteractions with immunecells[67]. By comprehensivelyunderstandingtheseinteractions, we can harnessthe full potential of disulfide-basedpolymericnanomaterials to benefit human health and theenvironment.

8 Environmental Fate and Impact

The examination of theenvironmentalbehavior of nanomaterials, including their fate in natural systems, is a critical aspect of understandingthepotentialconsequences of theirwidespread use in various applications. Nanomaterials, with theiruniqueproperties and versatility, have thepotential to bring significant benefits to society, but theirenvironmental impacts cannot be overlooked. This section looks into theintricate inter play betweennanomaterials and theenvironment, shedding light on theenvironmental fate and impact of these materials [68].

The environmentalfate of nanomaterials refers to theirjourney from production and use to theirultimatepresence in natural systems. This journeyencompasses various stages, including synthesis, manufacturing, application, transport, and disposal. Understanding how nanomaterials behave at each of these stages is crucial for assessingtheirenvironmental impact [69]. One of the primary challenges in assessingtheenvironmental fate of nanomaterials is their diverse composition and physical properties. Nanomaterials can vary widely in terms of size, shape, surfacecharge, and chemical composition. These variations can significantly influencetheirbehavior in theenvironment. For example, nanoparticles may be more mobile in soil and groundwater due to their small size, whilellargernanomaterials may settle more quickly in aquatic systems[70].Surfacecharge and functionalization can also impact how nanomaterialsinteract with environmentalmatrices and organisms. Nanomaterialsareintroduced into theenvironment through different pathways, depending on their applications. In thecontext of disulfide-basedpolymericnanomaterials, which are often used in drug delivery, biomedicine, and environmentalremediation, therearespecific pathways of introduction and potentialenvironmentalconsequences to consider[71]. In drug delivery, nanocarriers containing therapeuticagentsare designed to deliver drugs to target sites within the body with precision and reducedsideeffects. Whenthese nano carriersareadministered, there is a potential for some of them to be excreted and enter waste watersystems. This introducesthenanomaterials into aquatic environments, and their fate in thesesystemsdepends on factors such as theirsize, surfaceproperties, and the surrounding chemistry[72]. Disulfide-basedpolymericnanomaterials, which are known for their redox responsiveness, may undergo structural changes in response to the redox environment of the body or theenvironment. For instance, they may release their cargo in response to variations in the redox potential. Understandingthese transformations is vital to assesstheirenvironmental fate accurately. The ultimate fate of nanomaterials in natural systems can vary widely[4]. In some cases, they may be retained in sediments, soils, or aquatic systems, while in othercases, they may undergo transformations, including aggregation, dissolution, or surface modifications. These changes can influencethenanomaterials' bioavailability and toxicity to organisms in theenvironment.

One crucial aspect of assessingtheenvironmental fate of nanomaterials is understandingtheirpotential for bioaccumulation and biomagnification. Bioaccumulation refers to the accumulation of nanomaterials in organisms, while biomagnification refers to theprocess by which nanomaterials move up the food chain as predatorsconsumeprey[73]. The potential for bioaccumulation and biomagnification depends on thenanomaterial'sproperties, including size, surfacechemistry, and thespecificenvironmental conditions. Theenvironmental impact of nanomaterialsencompassestheirpotentialeffects on ecosystems, organisms, and human health. It is crucial to evaluatethese impacts comprehensively to make informed decisions about their use and regulation[74]. In thecase of disulfide-basedpolymericnanomaterials, several key considerations should be addressed. Disulfide-basedpolymericnanomaterials can interact with a variety of organisms in theenvironment, ranging from microorganisms to higher-level predators[75]. Understandingtheirecotoxicity is essential to assesstheir impact on ecosystems. Studies have shown that nanomaterials can affectthe growth, reproduction, and behavior of various aquatic and terrestrialspecies[68]. In caseswherenanomaterialsentertheenvironment and the food chain, there is a potential for human exposure. Ensuring thesafety of these materials is crucial, as exposure to certainnanomaterials can have adversehealtheffects. Comprehensive risk assessmentsarenecessary to evaluatepotentialhealth risks associated with disulfide-basedpolymericnanomaterials[76]. The redox responsiveness of disulfide-basedpolymericnanomaterials may lead to their transformation in theenvironment. Understandingtheextent and implications of these transformations is essential for assessingtheir long-term impact on ecosystems and human health. In thecontext of environmentalremediation, disulfide-basedpolymericnanomaterialsare designed to alleviate pollution and environmentalissues[77]. Whiletheir use can have positive impacts, it is essential to considerpotentialunintendedconsequences and sideeffects. Ensuring theeffectiveness and safety of these materials in remediationefforts is critical. Effectiveregulation of nanomaterials in theenvironment is challenging due to their diverse properties and applications. It is essential for regulatorybodies to stay informed about the latest research and develop guidelines and standards to ensuretheresponsible use of nanomaterials.

8.1 Assessment of PotentialEnvironmental Impacts, Including Effects on Ecosystems and Organisms

As the utilization of nanomaterialscontinues to expand across various industries, it becomes increasingly important to assesstheirpotentialenvironmental impacts, with a specific focus on theireffects on ecosystems and organisms. Nanomaterials, including disulfide-basedpolymericnanomaterials, possessuniqueproperties that can offer substantial benefits in applications such as environmentalremediation and pollution control. However, their introduction into theenvironmentraisesconcerns about theirinteractions with living organisms and ecosystems[78]. This assessment aims to delve into the key aspects of evaluatingthepotentialenvironmental impacts of nanomaterials, shedding light on theintricaterelationshipsbetweentheseengineered materials and the natural world. Understandingtheenvironmental impacts of nanomaterials begins with a consideration of their fate and transport in natural systems. Nanomaterials may entertheenvironment through various pathways, including industrial effluents, wastewaterdischarges, and the release of consumer products [79]. Once released, theirbehavior in theenvironmentdepends on factors likesize, shape, surfacecharge, and chemical composition. For disulfide-basedpolymericnanomaterials, their redox responsiveness can influencetheir fate, as they may degrade or transform in response to changing environmental conditions.

The transport of nanomaterials through terrestrial and aquatic ecosystems can lead to exposure of various organisms. This transport may occur through soil, sediment, or water, depending on thespecificproperties of thenanomaterials and theenvironmental conditions. Understandingtheseprocesses is crucial for assessingthepotential risks associated with their release and their impact on ecosystems and organisms [79]. Nanomaterials have thepotential to interact with a wide range of organisms, from microorganisms and plants to invertebrates and vertebrates. Their small size and high surfacearea can enhancethereactivity, and certainnanomaterials may exert toxic effects on living organisms (figure 8). Ecotoxicological studiesareessential for determiningthe impact of nanomaterials on various species and ecosystems[80].

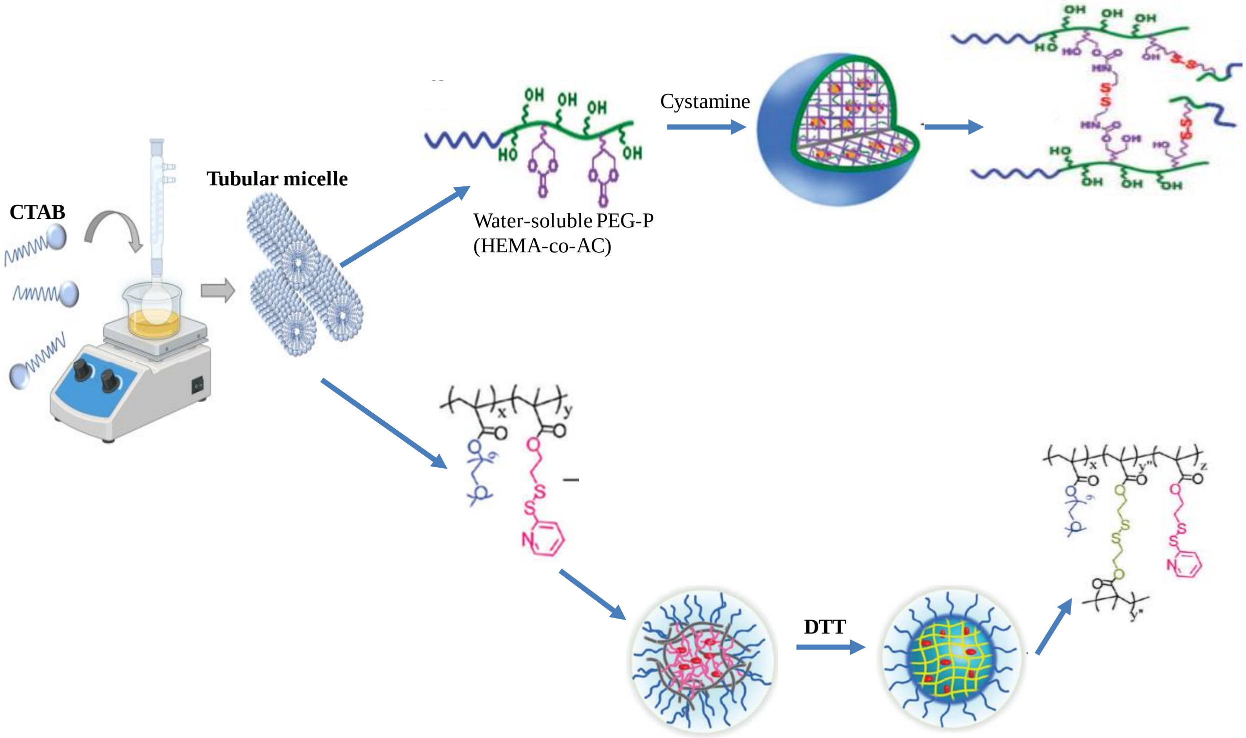

Figure 8 Disulfide-crosslinked nanoparticles prepared by self-assembly of amphiphilic block-co-polymers containing hydrophobic cyclic carbonate.

In thecontext of disulfide-basedpolymericnanomaterials, it is important to considertheirredoxsensitivity. While this property can be beneficial for controlled drug delivery in biomedical applications, it may also pose risks in theenvironment. The release of potentiallyreactivespecies or degradation products from thesenanomaterials could haveunintendedconsequences, affectingthehealth and survival of aquatic and terrestrial organisms [31]. Therefore, it is essential to investigatethepotentialecotoxicologicaleffects of disulfide-basedpolymericnanomaterials and determinetheir toxicity thresholds. The impacts of nanomaterials on ecosystemsextendbeyond individual organisms. Ecosystem-leveleffects can occur as a result of changes in species composition, food web dynamics, and nutrient cycling. For example, thepresence of nanomaterials in aquatic ecosystems may affect primary producers (e.g., phytoplankton) and subsequently impact higher trophic levels, including fish and other aquatic organisms [80]. Moreover, nanomaterials can influencenutrient dynamics by altering the availability of essentialelements, such as phosphorus and nitrogen, in ecosystems. To assess and mitigatethepotentialenvironmental impacts of nanomaterials, a comprehensive risk assessmentframework is necessary[81]. This framework should includeexposureassessment, hazard identification, dose-responsecharacterization, and risk characterization. In thecase of disulfide-basedpolymericnanomaterials, it is important to identifyspecificexposure pathways and levels, as well as potential hazards associated with theirredox-responsivebehavior. Dose-responserelationships should be established to determinesafeexposure levels, and risk characterization should inform decision-making and regulatory actions.

Mitigation strategies can includeengineeringinterventions to preventthe release of nanomaterials into theenvironment, such as improved containment and waste managementpractices. Additionally, designing nanomaterials with reduced toxicity and environmentalpersistence can contribute to safer use. Implementingresponsiblenanomaterial disposal and recycling practices is also crucial to minimize long-term environmental impacts.

Conclusion

In conclusion, this review provides a comprehensive understanding of the biological and environmental aspects of disulfide-based polymeric nanomaterials. By addressing the outlined objectives, it offers insights for researchers, policymakers, and practitioners in nanotechnology, biomedicine, and environmental science, contributing to the informed and ethical utilization of these materials for societal benefit while minimizing potential risks.

1 S. Bayda, M. Adeel, T. Tuccinardi, M. Cordani and F. Rizzolio, *Molecules*, , DOI:10.3390/molecules25010112.

2 L. Liu and P. Liu, *Front. Mater. Sci.*, 2015, **9**, 211–226.

3 N. Joudeh and D. Linke, *J. Nanobiotechnology*, 2022, **20**, 262.

4 S. K. Murthy, *Int. J. Nanomedicine*, 2007, **2**, 129–41.

5 S. Y. Lim, W. Shen and Z. Gao, *Chem. Soc. Rev.*, 2015, **44**, 362–381.

6 W. Li and X. Chen, *Nanomedicine*, 2015, **10**, 299–320.

7 A. Roy, A. Sharma, S. Yadav, L. T. Jule and R. Krishnaraj, *Bioinorg. Chem. Appl.*, 2021, **2021**, 1–16.

8 F. Albalawi, M. Z. Hussein, S. Fakurazi and M. J. Masarudin, *Int. J. Nanomedicine*, 2021, **16**, 161–184.

9 O. C. J. Andrén and M. Malkoch, *Polym. Chem.*, 2017, **8**, 4996–5001.

10 Y. Xia, F. Zhou, W. Hao and S. Tang, *Polymers (Basel).*, 2023, **15**, 3101.

11 P. J. Hogg, *Redox Rep.*, 2002, **7**, 71–77.

12 J. K. Patra, G. Das, L. F. Fraceto, E. V. R. Campos, M. D. P. Rodriguez-Torres, L. S. Acosta-Torres, L. A. Diaz-Torres, R. Grillo, M. K. Swamy, S. Sharma, S. Habtemariam and H.-S. Shin, *J. Nanobiotechnology*, 2018, **16**, 71.

13 Y. Malam, E. J. Lim and A. M. Seifalian, *Curr. Med. Chem.*, 2011, **18**, 1067–1078.

14 P. C. Ray, H. Yu and P. P. Fu, *J. Environ. Sci. Health. C. Environ. Carcinog. Ecotoxicol. Rev.*, 2009, **27**, 1–35.

15 M. Pięta, V. B. Purohit, J. Pietrasik and C. M. Plummer, *Polym. Chem.*, 2023, **14**, 7–31.

16 L. A. Pérez, R. Hernández, J. M. Alonso, R. Pérez-González and V. Sáez-Martínez, *Biomedicines*, 2021, **9**, 1113.

17 R. Devi, S. Singh, V. S. Rana, O. Singh, K. Kumar, R. Shrivastava, R. K. Yadav, A. K. Singh, N. K. Gupta and A. P. Singh, *J. Photochem. Photobiol. A Chem.*, 2024, **447**, 115248.

18 K. Pulka-Ziach, *J. Pept. Sci.*, , DOI:10.1002/psc.3096.

19 W. Lin, T. Sun, Z. Xie, J. Gu and X. Jing, *Chem. Sci.*, 2016, **7**, 1846–1852.

20 M. J. Heffernan and N. Murthy, *Ann. Biomed. Eng.*, 2009, **37**, 1993–2002.

21 R. Rezaei, M. Safaei, H. R. Mozaffari, H. Moradpoor, S. Karami, A. Golshah, B. Salimi and H. Karami, *Open access Maced. J. Med. Sci.*, 2019, **7**, 1884–1890.

22 J. Han, D. Zhao, D. Li, X. Wang, Z. Jin and K. Zhao, *Polymers (Basel).*, 2018, **10**, 31.

23 H. M. Mansour, M. Sohn, A. Al-Ghananeem and P. P. Deluca, *Int. J. Mol. Sci.*, 2010, **11**, 3298–322.

24 B. A. Witika, P. A. Makoni, S. K. Matafwali, B. Chabalenge, C. Mwila, A. C. Kalungia, C. I. Nkanga, A. M. Bapolisi and R. B. Walker, *Nanomater. (Basel, Switzerland)*, , DOI:10.3390/nano10091649.

25 A. Corma, T. Ródenas and M. J. Sabater, *Chem. Sci.*, 2012, **3**, 398–404.

26 H. Liu, R. Jian, H. Chen, X. Tian, C. Sun, J. Zhu, Z. Yang, J. Sun and C. Wang, *Nanomaterials*, 2019, **9**, 950.

27 C. Wiedemann, A. Kumar, A. Lang and O. Ohlenschläger, *Front. Chem.*, , DOI:10.3389/fchem.2020.00280.

28 H. K. Makadia and S. J. Siegel, *Polymers (Basel).*, 2011, **3**, 1377–1397.

29 G. Paramasivam, V. V. Palem, T. Sundaram, V. Sundaram, S. C. Kishore and S. Bellucci, *Nanomater. (Basel, Switzerland)*, , DOI:10.3390/nano11123228.

30 X. Li, L. Wang, Y. Fan, Q. Feng and F. Cui, *J. Nanomater.*, 2012, **2012**, 1–19.

31 B. Begines, T. Ortiz, M. Pérez-Aranda, G. Martínez, M. Merinero, F. Argüelles-Arias and A. Alcudia, *Nanomater. (Basel, Switzerland)*, , DOI:10.3390/nano10071403.

32 A. Bruinink and R. Luginbuehl, 2011, pp. 117–152.

33 K. Zafar, K. M. Zia, R. M. Alzhrani, A. H. Almalki and S. Alshehri, *Polymers (Basel).*, , DOI:10.3390/polym14102091.

34 S. Saeidnia, A. Manayi and M. Abdollahi, *Curr. Drug Discov. Technol.*, 2016, **12**, 218–224.

35 P. Boutelier, *Chirurgie*, 1996, **121**, 589–96.

36 A. REMES and D. WILLIAMS, *Biomaterials*, 1992, **13**, 731–743.

37 S. Bhattacharya, Q. Zhang, P. L. Carmichael, K. Boekelheide and M. E. Andersen, *PLoS One*, 2011, **6**, e20887.

38 S. Sharma, R. Parveen and B. P. Chatterji, *Curr. Pathobiol. Rep.*, 2021, **9**, 133–144.

39 W. Najahi-Missaoui, R. D. Arnold and B. S. Cummings, *Int. J. Mol. Sci.*, 2020, **22**, 385.

40 C.-T. Ng, J. J. Li, B.-H. Bay and L.-Y. L. Yung, *J. Nucleic Acids*, , DOI:10.4061/2010/947859.

41 D. M. Beaupre and R. G. Weiss, *Molecules*, , DOI:10.3390/molecules26113332.

42 M. Elmowafy, K. Shalaby, M. H. Elkomy, O. A. Alsaidan, H. A. M. Gomaa, M. A. Abdelgawad and E. M. Mostafa, *Polymers (Basel).*, 2023, **15**, 1123.

43 W. H. De Jong and P. J. A. Borm, *Int. J. Nanomedicine*, 2008, **3**, 133–49.

44 Q. Jiao, L. Li, Q. Mu and Q. Zhang, *Biomed Res. Int.*, 2014, **2014**, 426028.

45 E. O. Erhirhie, C. P. Ihekwereme and E. E. Ilodigwe, *Interdiscip. Toxicol.*, 2018, **11**, 5–12.

46 C. Egbuna, V. K. Parmar, J. Jeevanandam, S. M. Ezzat, K. C. Patrick-Iwuanyanwu, C. O. Adetunji, J. Khan, E. N. Onyeike, C. Z. Uche, M. Akram, M. S. Ibrahim, N. M. El Mahdy, C. G. Awuchi, K. Saravanan, H. Tijjani, U. E. Odoh, M. Messaoudi, J. C. Ifemeje, M. C. Olisah, N. J. Ezeofor, C. J. Chikwendu and C. G. Ibeabuchi, *J. Toxicol.*, 2021, **2021**, 9954443.

47 K. A. Altammar, *Front. Microbiol.*, 2023, **14**, 1155622.

48 D. M. Teleanu, C. Chircov, A. M. Grumezescu, A. Volceanov and R. I. Teleanu, *J. Clin. Med.*, , DOI:10.3390/jcm7120490.

49 R. Gupta and H. Xie, *J. Environ. Pathol. Toxicol. Oncol.*, 2018, **37**, 209–230.

50 S. Murugadoss, L. Godderis, M. Ghosh and P. H. Hoet, *Nanomater. (Basel, Switzerland)*, ,

DOI:10.3390/nano11071793.

51 R. Bajracharya, J. G. Song, B. R. Patil, S. H. Lee, H.-M. Noh, D.-H. Kim, G.-L. Kim, S.-H. Seo, J.-W. Park, S. H. Jeong, C. H. Lee and H.-K. Han, *Drug Deliv.*, 2022, **29**, 1959–1970.

52 Y. Totsuka, T. Higuchi, T. Imai, A. Nishikawa, T. Nohmi, T. Kato, S. Masuda, N. Kinae, K. Hiyoshi, S. Ogo, M. Kawanishi, T. Yagi, T. Ichinose, N. Fukumori, M. Watanabe, T. Sugimura and K. Wakabayashi, *Part. Fibre Toxicol.*, 2009, **6**, 23.

53 J.-M. Exbrayat, E. N. Moudilou and E. Lapied, *J. Nanotechnol.*, 2015, **2015**, 1–10.

54 C. Li and M. Tang, *J. Appl. Toxicol.*, 2024, **44**, 152–164.

55 I. Rusyn and G. P. Daston, *Environ. Health Perspect.*, 2010, **118**, 1047–50.

56 C. Gambardella and A. Pinsino, *Toxics*, , DOI:10.3390/toxics10070393.

57 G. A. Van Norman, *JACC. Basic to Transl. Sci.*, 2016, **1**, 399–412.

58 L. Yildirimer, N. T. K. Thanh, M. Loizidou and A. M. Seifalian, *Nano Today*, 2011, **6**, 585–607.

59 T. R. Kyriakides, A. Raj, T. H. Tseng, H. Xiao, R. Nguyen, F. S. Mohammed, S. Halder, M. Xu, M. J. Wu, S. Bao and W. C. Sheu, *Biomed. Mater.*, , DOI:10.1088/1748-605X/abe5fa.

60 M. Goldberg, R. Langer and X. Jia, *J. Biomater. Sci. Polym. Ed.*, 2007, **18**, 241–68.

61 M. Luconi, M. A. Sogorb, U. R. Markert, E. Benfenati, T. May, S. Wolbank, A. Roncaglioni, A. Schmidt, M. Straccia and S. Tait, *Int. J. Environ. Res. Public Health*, , DOI:10.3390/ijerph192315828.

62 Y.-W. Huang, M. Cambre and H.-J. Lee, *Int. J. Mol. Sci.*, , DOI:10.3390/ijms18122702.

63 A. Sadeghi, S. PourEskandar, E. Askari and M. Akbari, *Gels (Basel, Switzerland)*, , DOI:10.3390/gels9080632.

64 Z. Poon, S. Chen, A. C. Engler, H. Lee, E. Atas, G. von Maltzahn, S. N. Bhatia and P. T. Hammond, *Angew. Chem. Int. Ed. Engl.*, 2010, **49**, 7266–70.

65 H. Bahadar, F. Maqbool, K. Niaz and M. Abdollahi, *Iran. Biomed. J.*, 2016, **20**, 1–11.

66 D. Boraschi, D. Li, Y. Li and P. Italiani, *Int. J. Environ. Res. Public Health*, , DOI:10.3390/ijerph182211769.

67 J. S. Suk, Q. Xu, N. Kim, J. Hanes and L. M. Ensign, *Adv. Drug Deliv. Rev.*, 2016, **99**, 28–51.

68 S. J. Klaine, P. J. J. Alvarez, G. E. Batley, T. F. Fernandes, R. D. Handy, D. Y. Lyon, S. Mahendra, M. J. McLaughlin and J. R. Lead, *Environ. Toxicol. Chem.*, 2008, **27**, 1825–51.

69 J. K. Patra and K.-H. Baek, *J. Nanomater.*, 2014, **2014**, 1–12.

70 L. Wang, W.-M. Wu, N. S. Bolan, D. C. W. Tsang, Y. Li, M. Qin and D. Hou, *J. Hazard. Mater.*, 2021, **401**, 123415.

71 D. R. Baer, M. H. Engelhard, G. E. Johnson, J. Laskin, J. Lai, K. Mueller, P. Munusamy, S. Thevuthasan, H. Wang, N. Washton, A. Elder, B. L. Baisch, A. Karakoti, S. V. N. T. Kuchibhatla and D. Moon, *J. Vac. Sci. Technol. A.*, 2013, **31**, 50820.

72 G. C. N. B. Lôbo, K. L. R. Paiva, A. L. G. Silva, M. M. Simões, M. A. Radicchi and S. N. Báo, *Pharmaceutics*, , DOI:10.3390/pharmaceutics13081167.

73 M. Li, Y. Zhang, S. Feng, X. Zhang, Y. Xi and X. Xiang, *Ecotoxicology*, 2022, **31**, 1023–1034.

74 G. Martínez, M. Merinero, M. Pérez-Aranda, E. M. Pérez-Soriano, T. Ortiz, B. Begines and A. Alcudia, *Mater. (Basel, Switzerland)*, , DOI:10.3390/ma14010166.

75 V. A. Spirescu, C. Chircov, A. M. Grumezescu and E. Andronescu, *Polymers (Basel).*, , DOI:10.3390/polym13050724.

76 G. H. Dewar, J. K. Kwakye, R. T. Parfitt and R. Sibson, *J. Pharm. Sci.*, 1982, **71**, 802–6.

77 S. Sahoo, A. Gopalan, S. Ramesh, P. Nirmala, G. Ramkumar, S. Agnes Shifani, R. Subbiah and J. Isaac JoshuaRamesh Lalvani, *Adv. Mater. Sci. Eng.*, 2021, **2021**, 1–9.

78 M. L. Del Prado-Audelo, I. García Kerdan, L. Escutia-Guadarrama, J. M. Reyna-González, J. J. Magaña and G. Leyva-Gómez, *Front. Environ. Sci.*, , DOI:10.3389/fenvs.2021.793765.

79 E. A. Kumah, R. D. Fopa, S. Harati, P. Boadu, F. V. Zohoori and T. Pak, *BMC Public Health*, 2023, **23**, 1059.

80 K. Nadarajah and N. S. N. Abdul Rahman, *Int. J. Mol. Sci.*, , DOI:10.3390/ijms221910388.

81 Y. Sun, G. Zhu, W. Zhao, Y. Jiang, Q. Wang, Q. Wang, Y. Rui, P. Zhang and L. Gao, *Nanomater. (Basel, Switzerland)*, , DOI:10.3390/nano12234219.