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Perspectives on palladium-based nanomaterials: green synthesis, ecotoxicity, and risk assessment

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Palladium-based nanomaterials (Pd-NMs) have been mass produced and applied due to their remarkable properties and high earth abundance. This makes Pd-NMs come into frequent contact with the environment and enter the ecological environment. Comparative analysis of the toxicological data revealed that Pd-NMs have acute or chronic toxicity in both *in vitro* and *in vivo* biological receptors models, but only limited information has been provided on the possible environmental migration and transformation or concentration distribution in the environmental media of Pd-NMs. Therefore, a perspective is needed of the existing data to provide a more professional and comprehensive assessment of their ecotoxicity and sustainable development. This perspective describes the critical knowledge needed to assess their ecological risks. We recommend focusing on the current and future concentration and distribution of Pd-NMs in the environment, guiding the assessment of the full-cycle ecotoxicity of Pd-NMs, and strongly encourage the quantitative measurement of the concentration level of Pd-NMs in the real environment.

Environmental significance

As nanomaterials develop, it is important to consider their effects on organisms and ecosystems and so environmental protection and sustainable development need to be aimed for. Therefore, a comprehensive assessment of the ecological risk of the rapidly developing nanomaterials is needed. This perspective analyzes and discusses the full life cycle, ecotoxicity, and assessment methods and provides recommendations for the sustainable development of palladium-based nanomaterials and other similar or related nanomaterials.

Introduction

In recent decades, nanoscience has made major breakthroughs and has greatly improved the human life.[1–3] As an important achievement of nanoscience, nanomaterials are produced and used in many technologies and consumer products owing to their inimitable properties.[4–6] Among these, metal-based nanomaterials (M-NMs) have attracted widespread attention owing to their widespread application prospects.[7] In particular, noble M-NMs are widely used in the fields of catalysis,[8] environmental remediation,[9,10] sensors,[11,12] nanomedicine,[13,14] and so on.[15–17] However, it is challenging to ensure sustainability from the synthesis of products and to their applications and disposal.[18–20]

Palladium-based nanomaterials (Pd-NMs) are one of the most widely used noble M-NMs. Pd-NMs offer opportunities as efficient catalyst materials due to their high specific surface area, abundant active sites, and high catalytic activity.[21–23] Trends in publishing activities highlight the continuous development of Pd-NMs and related materials. Pd-NMs have valuable catalytic and optical properties, which provide extensive opportunities for their chemical, medical, and environmental applications in human activities.[23–25] However, growth in the use of Pd-NMs has been accompanied by their increasing exposure to the ecological environment. In contrast, toxicology research of Pd-NMs and the related materials is far behind their applications, but such a toxicological study would have a positive significance for their sustainable development and to ensure environmental protection from their use.

With the rapid development of Pd-NMs and related and/or similar materials, a variety of different voices have emerged in the public. On the one hand, Pd-NMs are favored by engineers in the fields of material, chemical, and energy science because of their excellent characteristics (Fig. 1).[24,26,27] On the other hand, with the extensive application of Pd-NMs, the increasing interaction between Pd-NMs and the ecological environment makes individuals in the field of environmental ecology and biomedicine worry that Pd-NMs may violate the principle of sustainable development and

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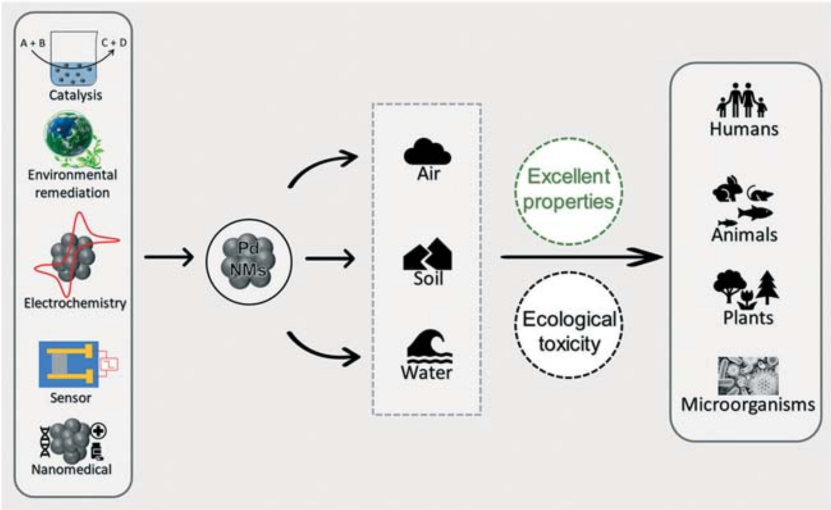

Fig. 1 Diagram summary of the applications, environmental behavior, and ecological risk of Pd-NMs.

may cause ecological harm (Fig. 1).[28,29] To better protect the ecological environment, we need to control the usage amount of Pd-NMs and improve the techniques and methods used for assessing their toxicity.

In 2015, Chen and Ostrom introduced in detail various synthesis methods of Pd-NMs, as well as discussing their outstanding properties and wide application range.[24] Pd-NMs have unique chemical and catalytic properties, and their synthesis and application are expected to see remarkable growth over the next decade. Especially in the biomedical field, the need for real-time care and monitoring will accelerate the emergence of these materials.[30–32] Pd-NMs that are released into the environment or in contact with organisms initially exist as nanoparticles (NPs), which may subsequently migrate, transform, and accumulate in the environment or in organisms, ultimately causing harm to the organisms. Existing data lack a full assessment of the biological activity of Pd-NMs, and toxicity is often neglected by folks in the design of new nanomaterials, where the outstanding properties are regarded as the only selling point of a new material system. Consequently, Egorova and Ananikov called for specific measurements of special metal catalysts, including Pd-NMs, and for their nature, toxicity, bioavailability, and possible exposure pathways to be taken into account in the development and application of these chemicals.[33]

Meanwhile, Leso and Iavicoli critically analyzed data from the existing literature on the toxicological and occupational risk assessment of Pd-NMs, and pointed out the negative effects of these chemicals on the ecosystem function for use in determining appropriate strategies to assess and manage the occupational risk related to these materials.[34] For gaining a more comprehensive understanding of the toxicology of Pd-NMs and to provide guidance for their sustainable development, the current perspective summarizes and analyzes the risks of Pd-NMs on the environment, and discusses the *in vitro* and *in vivo* research problems related to Pd-NMs. This perspective aim to describe the ecotoxicological effects of Pd-NMs and proposes that individuals should consider the potential environmental hazards of these nanomaterials while at the same time promoting their use. The insights of this perspective apply not only to Pd-NMs but also to other similar and related M-NMs. Their excellent properties or toxicity cannot be used as the sole reason for promoting new nanomaterials or hindering their development without a proper comprehensive and dedicated evaluation.

Environmental impact of palladium-based nanomaterials

Exploration of the scalable production routes

Here, the question to ask is, "are there multiple synthesis routes and are some more sustainable that the others?" There are multiple routes to prepare Pd-NMs (such as nanofilms, nanowires, nanocrystals, nanotubes, nanospheres, nanorods, *etc.*), including physical synthesis methods (such as sputtering, ion or electron beam deposition, and laser ablation),[35–37] hydrothermal methods (one-step synthesis),[38] electrochemical deposition,[39] chemical deposition,[40] and other methods (such as microemulsion[41] and photochemically[42] assisted synthesis). The important environmental impact of these synthetic methods include the need to use toxic reaction reagents and the production of toxic by-products.

Compared to other reaction reagents, polyols have unparalleled advantages.[43] First, alcohols have multifunctional properties, such as being able to act as a reducing agent, solvent, and stabilizer for metal precursors. Second, polyols have inherent hydrogen bond interaction and an adjustable number of –OH groups, which gives them an elastic structure. Meanwhile, due to the existence of hydrogen bond supramolecular structures, polyols can prevent the agglomeration of NPs.[44] Third, the physicochemical properties of different polyols are different, which facilitate them to meet the different synthetic conditions for the synthesis of Pd-NMs with different properties. To illustrate, Pd-NMs synthesized by a rapid reduction of ethylene glycol (EG) at a relatively high temperature usually have a cubic or rod-like single-crystal structure.[45] However, the use of other polyols and/or changing reaction conditions can affect the growth rates of different surfaces of Pd-NMs, thus affecting their shape.[46] Finally, noteworthily, polyols derived from environmentally friendly plant extracts are also outstanding substrates for the synthesis of Pd-NMs.[47–49]

To minimize secondary contamination in the preparation of Pd-NMs, the synthesis of Pd-NMs or other related novel nanomaterials in green media (such as plant extracts)[50–52] is beneficial for the sustainable development of nanomaterials. Green chemical substances in plant extract can be used as a reducing agent or stabilizer in the preparation process of Pd-NMs, which can simply and quickly reduce Pd metal ions to zero-valent Pd metal without agglomeration.[53–55] Noteworthily, these phytochemicals can not only greatly reduce the adverse environmental effects of the synthesis process, but can also ensure high reaction rates and controllable yields.[52,56] The actual method is based on the ability of phytochemical molecules to absorb, accumulate, transform, and recycle metal ions, which demonstrates the characteristics of economy, sustainability, and environmental protection.

In 2008, Varma *et al.*, one of the pioneers in this field, reported the green synthesis of a large number of Pd-NMs at room temperature using coffee and tea extracts.[57] The main components of these extracts were caffeine and polyphenols, which could form complexes with metal ions in solution and acted as reducing agents to reduce metal precursors to metals. Meanwhile, they could also be used as dispersants in the synthesis process to avoid the accumulation of metal NPs (MNPs). The synthesized Pd-NMs were mostly spherical in shape, but varied in size, depending on the quality and source of the extract (Fig. 2). Subsequently, Li *et al.* and Philip *et al.* extracted polyols from *Cinnamomum camphora* leaf[58] and dried leaf powder of *Anacardium occidentale*,[59] respectively, for the synthesis of Pd-NMs. They found the polyol component binds to the metal complex and is used to reduce the metal precursors, while the heterocyclic component stabilizes the reduced MNPs. Furthermore, they found the size of Pd NPs could be controlled by changing the concentration of Pd ions in the solution without the need for additional templates. Besides, *Cacumen platycladi* leaf extract,[60] *Pulicaria glutinosa* extract,[61] fruit and *Aloe vera* juices,[62] artichoke leaf extract,[63] *Catharanthus roseus* leaf extract,[64] and *Terminalia chebula* aqueous extract[65] have also been reported as reaction media for the simple and green synthesis of Pd-NMs.

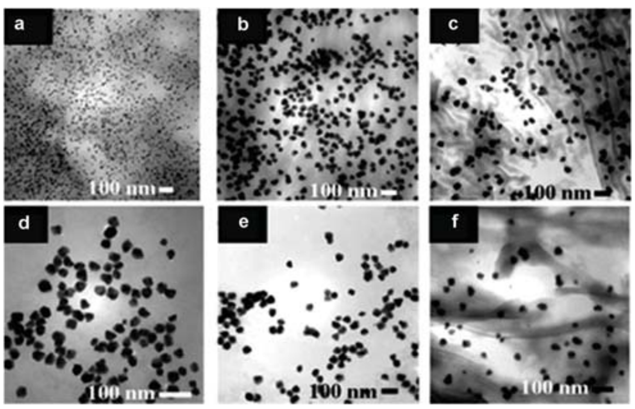

Fig. 2 TEM image of Pd NPs synthesized using: (a) Sanka coffee, (b) Bigelow tea, (c) Luzianne tea, (d) Starbucks coffee, (e) Folgers coffee, and (f) Lipton tea extract at room temperature in one step without using any hazardous reducing chemicals or non-degradable capping agents. Reprinted with permission from ref. 57. Copyright 2008 the Royal Society of Chemistry.

Release and transformation during use

Pd-NMs are characterized by their invaluable catalytic, mechanical, and optical properties, which may offer the opportunity for their application in human activities (Fig. 3), including electrochemical reactions,[66,67] nanomedicine,[68,69] fine chemistry,[70,71] sensors,[72,73] and especially in the treatment of environmental pollutants, such as to control harmful exhaust emissions of automobiles, eliminate indoor air pollutants, and treat wastewater.[74–78] The environmental concentration of Pd-NMs has prominently increased from these human activities. To illustrate, for catalytic applications, all types of Pd-based catalytic systems, even immobilized catalysts (including homogeneous, heterogeneous, metal complexes, and supported Pd-based catalysts), have been demonstrated to suffer from inevitable

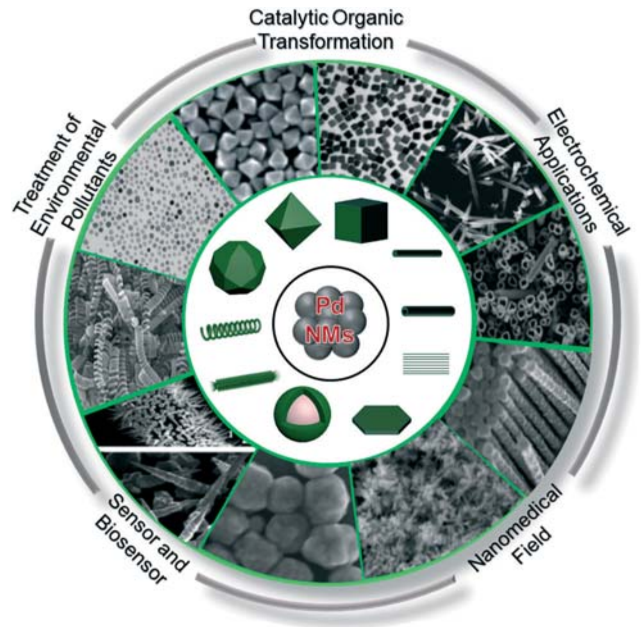

Fig. 3 The source composition of Pd-NMs and the electrochemical applications, catalytic organic transformation, the treatment of environmental contaminants, and use in sensors and nanomedicine.

leaching.[23,79,80] Leaching can cause metallic substances and NPs to be released directly or indirectly into the environment. When the diffused Pd-NMs come into contact with organic or inorganic ligands and water components, chemical reactions occur on the surface of Pd-NMs, resulting in morphological changes and the formation of core–shell Pd-NMs,[81] which further promotes environmental migration of the Pd-NMs.

Especially from the transportation sources, with the increase of car use in densely populated areas, an increase in the environmental concentration of Pd-NMs has been well documented.[82–84] Here, Pd-NMs used in automotive catalytic converters are discharged as particles in the exhaust gas and accumulate in the local soil.[85–87] Subsequently, through various chemical processes (such as redox reactions and complexation reactions), their environmental mobility is enhanced, eventually leading to their interactions with a variety of organisms.[88,89] Pd-NMs that enter an organism diffuse across cell membranes, and may end up in various organs or throughout the body through lymph and blood circulation.[90,91]

Accumulation and deposition of the nanomaterials cause damage to aquatic organisms in water environments.[92,93] Changes in the surface chemistry of NPs and the chemical properties of the aquatic environment can change the degree of aggregation and deposition of the nanomaterials.[94,95] Furthermore, combined effects of the environment, such as acid rain, could increase the solubility of Pd-NMs and spread them across the ecosystem through runoff or atmospheric transport.[96] In summary, Pd-NMs in the environment exhibit toxicity to plants, animals, and microorganisms (Fig. 4), and the environmental behavior of Pd-NMs could aggravate their ecological risk.[97]

Bioavailability and toxicity in organisms

Acute and chronic toxicity to animals

Pd-NMs have the highest bioavailability among platinum group metals and greater fluidity than other platinum group metals.[98,99] Pd-NMs have been proved to be enriched in living organisms and their retention in the organism depends on how it is administered.[28,100] Pd-NMs enter animals mainly by inhalation and injection, and exert cytotoxic and pro-inflammatory effects *in vitro* while they affected different target organs in an animal model test. The mechanisms of the toxicity of Pd-NMs in animal models are mainly related to the toxicity of released Pd ions and the animal's oxygen stress response, which disrupts the energy metabolism balance, inhibiting the transcription of RNA, damaging DNA, and cell inflammation (Fig. 4). For example, Pd^{2+} ions may be slowly absorbed by animal cells and distributed in the nucleus and mitochondria and can affect and inhibit enzyme systems in animal cells.[101]

Pd-NMs in contact with animals in the environment could enter the organism and be transformed. Pd initially is released as metal and oxide particles, but they can then be transformed in the environment, in the digestive tract, or in the cell compartment to produce more harmful soluble substances.[102] The main factors that determine the toxicity of Pd NPs in the air are related to the particle size and chemical composition, while inhalation routes are considered to pose a greater risk for health effects.[98] The metal forms of Pd-NMs that are drawn into the respiratory tract from the air are usually biologically inert, but some of the metal salts can become sensitized chlorine compounds, which are strong allergens and sensitizers.[103]

Pd-NMs have also displayed specific cross-sensitization with nickel and can penetrate through the skin.[29] As the surface-to-mass ratio of Pd-NMs increases, their biological activity increases, which in turn releases more active metal ions, ultimately leading to an increased likelihood of them penetrating the skin.[29] Noteworthily, compared with intact skin, damaged skin significantly increases the absorption of Pd-NMs (Fig. 5).[29] Pd content in the whole skin layer from the epidermis to dermis was found to be significantly decreased. Within the skin, these nanomaterials may have a long-term role and may be involved in sensitization or may be spread throughout the body.

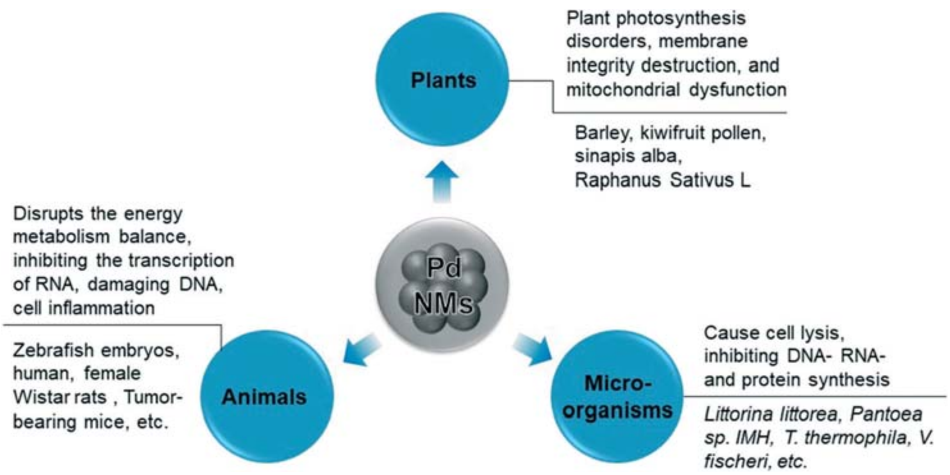

Fig. 4 The toxicity effects of Pd-NMs to plants, animals, and microorganisms.

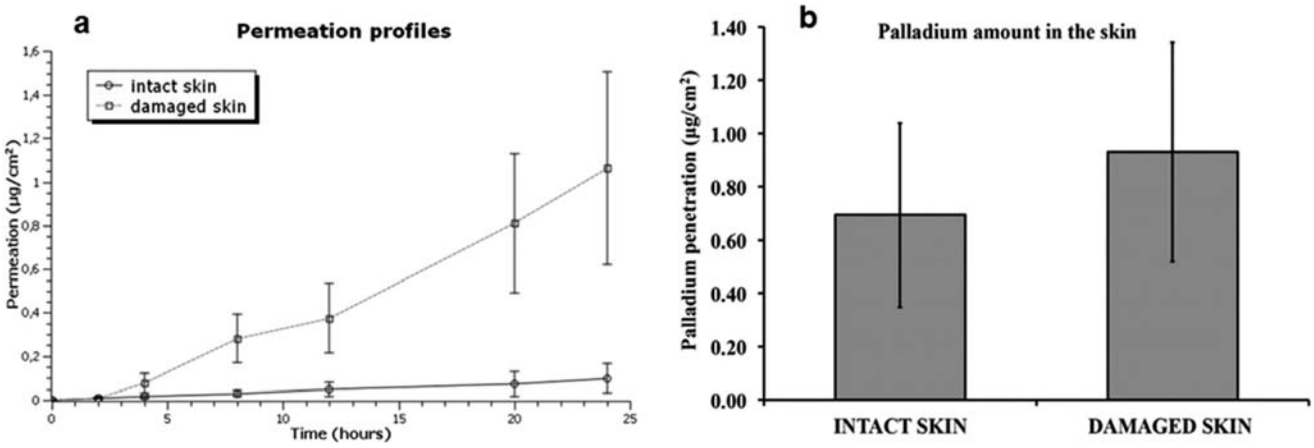

Fig. 5 (a) Permeation profile of Pd after the skin application of Pd NPs solution. (b) Mean values and standard deviations of Pd amounts (mg cm^{-2}) in intact and damaged skin. Reprinted with permission from ref. 29. Copyright 2016 Elsevier Science Ltd.

Significant cytotoxic effects of Pd-NMs have been observed in several human cell models, including respiratory cells,[87,104] cervical,[105] and liver.[106] Pd-NMs released into the environment can be inhaled by humans and can accumulate in the respiratory tract, and the absorption of Pd through the digestive tract has been shown to be insignificant.[107] Meanwhile, human exposure to Pd-NMs may cause strong sensitization reactions.[108,109] Furthermore, Pd-NMs that enter animals may accumulate in the liver, kidneys, lungs, and bones.[30,110] However, serum biochemical evaluation[110] showed no significant hepatotoxicity in mice after 7 days of intravenous injection of various Pd-NMs (Fig. 6a). Moreover, no significant damage from Pd-NMs to the organs of mice within 28 days was observed in H&E stained images (Fig. 6b). Meanwhile and noteworthily, the toxicity of Pd-NMs is affected by multiple factors, among which the dose and time are the two main factors. Therefore, a systematic study of the ecotoxicity of Pd-NMs at different doses within different time periods (focusing on the long-term potential toxicity) is still required.

Soluble Pd-NMs have been found to have serious health effects on higher vertebrates in acute and chronic studies.[111] Soluble Pd-NMs can enter the mouse, rat, and rabbit body and can cause mitochondrial membrane potential disorder, arrhythmia, organ dysfunction, and even death.[112,113] Furthermore, the time of retention of Pd in the animals could affect the level of toxicity. Intratracheal or intravenous administration can lead to a prolonged retention time of Pd in animals more than in the oral administration of $PdCl_2$, resulting in a higher biological toxicity. Pd-NMs accumulated in living organisms may also be expelled from living organisms, and the main way for these MNPs to be eliminated is through urine and feces.[101] Several studies have shown that soluble Pd-NMs may also cause patient poisoning, such as by accumulating in organ tissues, especially in the kidneys, lungs, liver, spleen, bones, and

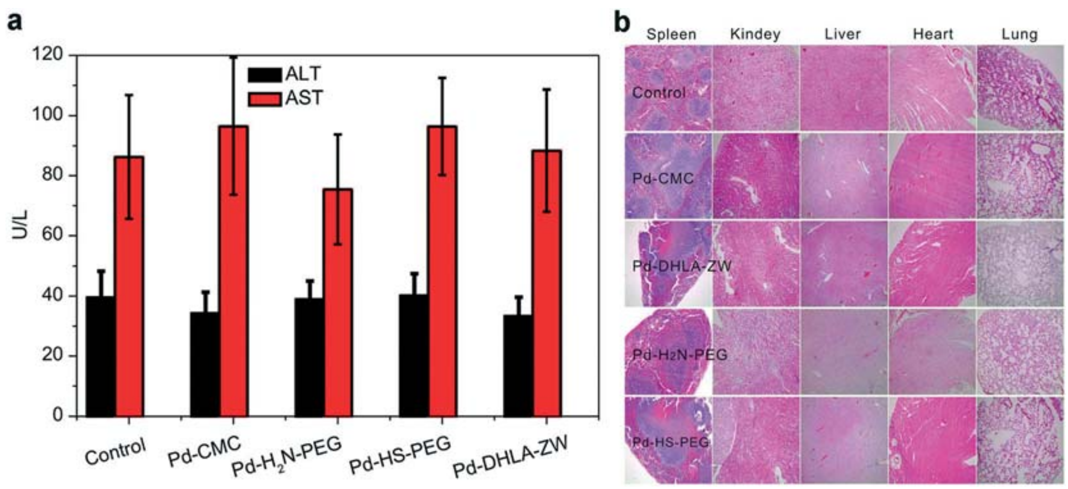

Fig. 6 (a) Serum biochemistry analysis of mice treated with different coated Pd NSs at 7 days post injection. (b) Photos of H&E stained diaphragm slices from the mice treated with different coated Pd NSs at 28 days post injection. Reprinted with permission from ref. 110. Copyright 2015 American Chemical Society.

heart.[114] Meanwhile, the mitochondria are important subcellular organelles for Pd-NMs toxicity.[112] Studies have shown that Pd-NMs toxicity is caused by the breakdown of the mitochondrial membrane potential and the depletion of cellular glutathione (GSH) levels,[115] which proposes that Pd-NMs are more susceptible to toxicity to kidney tissue than liver tissue. Histopathological findings in the kidney indicate that they change renal tubular epithelial, which further affects the glomerular filtration function.[116]

Furthermore, Pd-NMs can inhibit DNA and protein synthesis, and were found to damage different types of DNA in mouse lymphoma cell lines.[112] Pd-NMs can also inhibit the gene expression of multiple metal markers and induce the conformational changes and cleavage of DNA.[117] Meanwhile, Pd-NMs interfere with the inflammatory process by increasing the adhesion of eosinophils on endothelial cells at low concentrations.[118] More research is needed to further study the cellular and molecular mechanisms to help understand the process by which Pd-NMs induce allergies and inflammation.

To further understand the toxicity of Pd-NMs, the toxicity of Pd-NMs during embryonic development were investigated. Zebrafish have a high genetic similarity with humans. Zebrafish embryos have high optical clarity and can be screened on a large scale, and have a low operating cost, which make them powerful tools for environmental toxicity detection.[119] The molecular mechanism of Pd-NMs inducing embryonic morphological changes was investigated by using zebrafish as a model. The results propose that Pd treatment resulted in zebrafish embryo experiencing pericardial edema, inhibiting embryo survival and hatchability and resulting in embryonic pericardial edema and cardiac malformation (Fig. 7), which affected the expression levels of several cardiac-related genes and antioxidant enzymes, thereby revealing the underlying molecular mechanism of how Pd-NMs induce zebrafish embryonic heart malformations.[100]

In many cases, technical problems have prevented zebrafish model platforms from being fully established. First, zebrafish farming techniques are highly demanding, and changes in simple parameters, such as temperature, pH, and symbiotic microbes, can confuse the test results.[119] Second, so far, zebrafish models have focused on a limited range of environmental chemicals that are toxic at an early life stage.[120,121] Therefore, powerful new phenotypic techniques and systematic approaches to identify a wider range of chemicals are needed to investigate the toxic effects of a large number of environmental factors on zebrafish models throughout their life stages. Finally, if we want to maximize the use of zebrafish models to describe the toxicological reactions of higher-level organisms, a more detailed understanding of the similarities between zebrafish and higher-level organisms is needed, including a combination of multichannel organ-specific studies, functional genomics, and automated image analysis techniques.[119] In summary, the zebrafish model as an explanatory tool in the field of toxicology is promising for the systematic exploration of nanomaterial–environment interactions. Also conceivably, with the establishment of a fully and robust zebrafish model platform, toxicity prediction and the development of new materials will eventually be synchronized.

Evaluation of phytotoxicity

There is a need to understand w the hazards to plants are of Pd-NMs entering the environment. Rare Pd-NMs have been extensively redistributed in the biosphere as a result of human activity. Lethal toxicity and cytotoxicity of Pd-NMs in terrestrial plants are developing rapidly. There is a serious lack of public awareness of the environmental hazards caused by the widespread use of trace nano-metal pollutants.

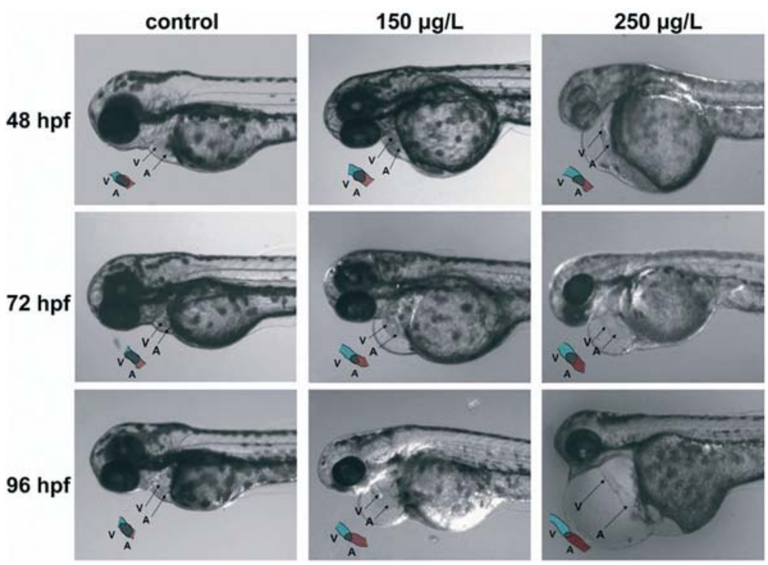

Fig. 7 Pd caused pericardial edema and cardiac malformation in zebrafish embryos. Reprinted with permission from ref. 100. Copyright 2014 Elsevier Science Ltd.

In a natural state, plants have less contact with rare metals and fewer resistance mechanisms than those found in some organisms.[122] Therefore, to promote the application of these materials, it is necessary to investigate the harm they cause in plants.

For understanding the ecological toxicological effects of Pd-NMs on plants, it was found that Pd-NMs can quickly enter the kiwifruit plant in large quantities, change the shape of pollen, and cause a rapid loss of endogenous calcium in pollen grains, which would result in pollen plasma membrane damage.[123,124] Moreover, Pd-NMs affect plant growth,[125] and seeds germination,[126] but no effect of Pd NPs on plant growth was observed within 15 days of plant culture, suggesting that NPs may not directly affect plant growth but may do indirectly.[126] Further research is needed to understand whether environmental soil exposure to rare Pd NPs has a short-term or long-term impact on crop production, as well as the specific toxicity mechanisms. In this regard, pollens are highly sensitive to environmental pollutants, which would be helpful for the accurate detection of the effects of Pd-NMs on biological systems.

Taking kiwi pollen as an example, studies have found that Pd-NMs enter the kiwi pollen grains faster and more than just soluble Pd(II) enters (Fig. 8a and b).[123] Compared with the effect of soluble Pd(II), under the granular action of a low concentration of Pd, the endogenous calcium of kiwifruit pollen is rapidly lost (Fig. 8c and d), thereby causing damage to the pollen plasma membrane, which seriously inhibits the growth of pollen tubes. The toxicity of Pd-NMs to plants is largely caused by the reactive oxygen species (ROS) production,[122] which can result in plant photosynthesis disorders, membrane integrity destruction, and mitochondrial dysfunction by attacking the interactions of cell membranes, proteins, lipids, and DNA in cells (Fig. 4).

Damage to microorganisms

Microorganisms complete the cycle of various trace elements and thus are often the common target of environmental toxicology research.[127–129] The toxicology of Pd catalysts was explored using the marine bacteria *V. fischeri* as a model.[130] *V. fischeri* were cultured by designing a microenvironment that simulated the actual sampling location. During the culture process, the effects of different concentrations of Pd-NMs on respiratory metabolism were reported, and no side effects were found (Fig. 9).[130] Meanwhile, the effect of Pd-NMs on the structure of a polychlorinated biphenyl (PCB)-dechlorinated microbial community, which was enriched from marine sediment, has also been reported.[130] Investigations found that the Pd-NMs had no permanent impact on their community organization, and even, on the contrary, increased the biodiversity of microbial communities. All in all, the results of this work counter the hypothesis that Pd-NMs affect marine microbial communities. This was the first comprehensive study of the effects of Pd-NMs on marine microbial communities and provided significant information for the assessment of the toxicity of Pd-NMs.

In the other example, the results showed that Pd-NMs cause genomic alterations in the freshwater green algae *Pseudokirchneriella subcapitata*,[131] which in turn caused great damage to the *Pseudokirchneriella subcapitata* by affecting the growth process and morphology. Compared with animals and plants, the mechanism of the toxicity of Pd-

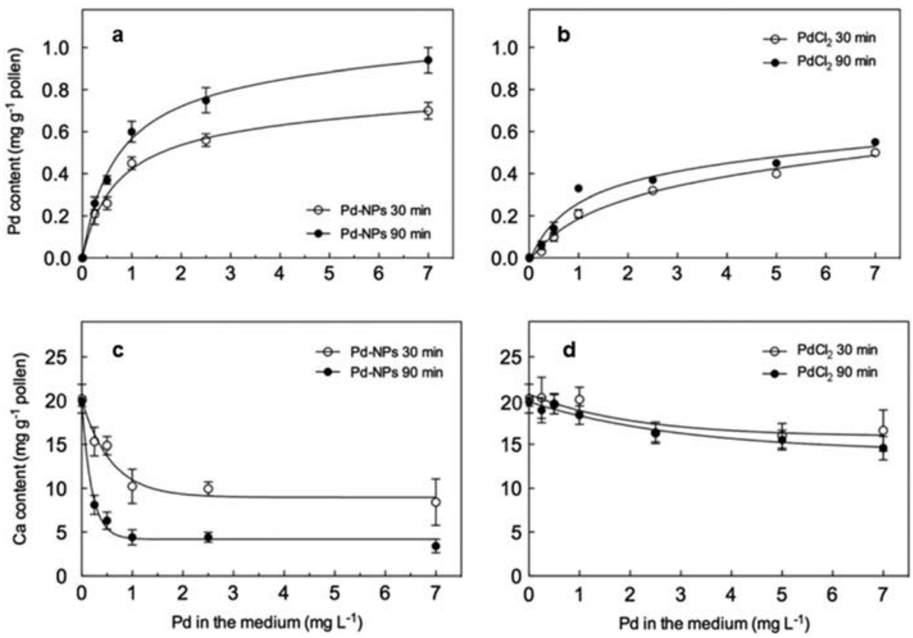

Fig. 8 Pd (a and b) and Ca (c and d) content in controls and in pollen treated for 30 and 90 min with increasing Pd concentrations administered as either Pd NPs (a and c) or $PdCl_2$ (b and d). Reprinted with permission from ref. 123. Copyright 2009 Elsevier Science Ltd.

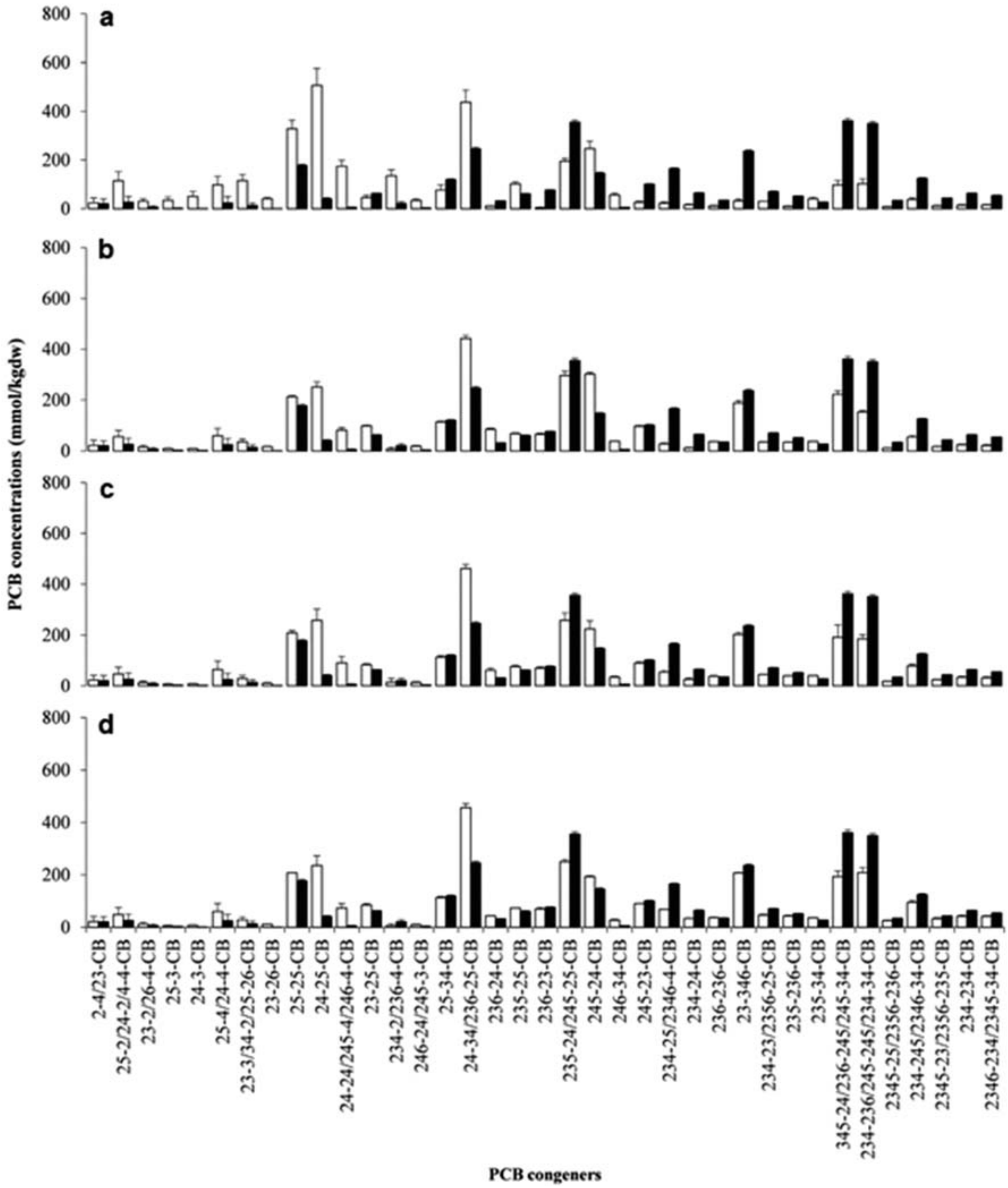

Fig. 9 Concentrations of spiked PCB congeners and their dechlorination products constituting more than 1% w/w of total PCBs at the end of incubation in biologically active (white bars) and sterile (black bars) sets of spiked microcosms. (a) Unamended microcosms; (b) hydrogen-amended microcosms; (c) microcosms amended with hydrogen + bio-Pd 5 mg kg^{-1} dw; (d) microcosms amended with hydrogen + bio-Pd 50 mg kg^{-1} dw. Values are the means of triplicate microcosms with error bars representing the standard deviation. Reprinted with permission from ref. 130. Copyright 2016 Elsevier Science Ltd.

NMs to microorganisms is mainly through the microbial community structure, growth, and diversity. The main mechanism of Pd-NMs to affect microorganisms is still through oxidative stress. Exposure to Pd-NMs in the environment produces ROS directly or indirectly, which then interact with membrane proteins and bacterial cell walls, and can cause cell lysis, inhibiting DNA-, RNA- and protein synthesis (Fig. 4).

Toxicity assessment methods and challenges

As described in the previous sections of this article, the toxicity of Pd-NMs to the ecosystem (cytotoxicity, genotoxicity, inflammatory response, oxidative stress response, and so on) has been demonstrated. Parallel studies and toxicity assessments of these nanomaterials are still needed before promoting their production and wide-scale application. However, the toxicity of Pd-NMs and/or other related nanomaterials and their interaction with ecosystems have not yet been systematically studied.[132–134] Currently, most methods of toxicity assessment have been developed based on chemical toxicity. Due to the unique properties of Pd-NMs, the results of these assessment methods may be disturbed.[106,135] Compared with traditional materials, the size, shape, specific surface area, doping degree, solubility, agglomeration state, crystallinity, and other characteristics of Pd-NMs may affect the characterization results of the biological effects.[136–138] Incomplete and inaccurate characterization could lead to incorrect assessment results. Besides, the non-development of unified and standardized assessment methods is not conducive to the comparison of the toxicity assessment results among different research groups.

The detection of Pd dispersed in the environment requires a sophisticated analytical method. Many techniques for detecting Pd in environmental samples have been developed.[139,140] To improve the sensitivity, it is feasible to combine the existing detection technology, such as gas chromatography-mass spectrometry (GC-MS) analysis.[141] Compared to conventional solid-phase extraction methods, this newly developed strategy can achieve a higher sensitivity by increasing the concentration of the maximum allowable coexisting heavy metal ions.

From the perspective of the toxicity test, *in vitro* toxicity testing is the primary method to study the ecotoxicity of Pd-NMs, because it is faster, easier, and does not pose ethical problems. However, toxicity studies of cultured cell systems *in vitro* do not clearly explain cell–cell and cell–stromal interactions, ignoring cell diversity, and lacking a consideration of the hormonal effects *in vivo*. Moreover, with *in vitro* experiments, it can be difficult to reflect the actual effect of the Pd-NMs *in vivo*.[142] Therefore, toxicity assessment also requires *in vivo* experiments, and *in vivo* experiments can also be used to study the long-term toxicity of Pd-NMs. Furthermore, pharmacokinetic studies help to maximize the interpretation of the correspondence between compounds in *in vivo* and *in vitro* investigations.[143–145] The pharmacokinetics of the Pd-NMs are helpful for a comprehensive quantitative analysis of the target tissues or cells acted on by the materials, the residence time *in vivo*, the toxicity time, and the dose, but before starting the pharmacokinetic study, a simulation should be performed of the Pd-NMs effect on organisms.

In terms of microbiological inhibition, the toxicological evaluation results of Pd-NMs are different under different experimental conditions and in different microbial communities. For example, Pd-NMs showed a strong growth inhibition effect on bacteria in the culture of a single microorganism.[146,147] However, in the simulated native microbial environment, as in the soil microbial system and the marine microbial system, the toxicity inhibition of Pd-NMs on the microbial community can be ignored.[126,130] This indicates that toxicity evaluation is multi-directional and environmental media can protect a microbial community and prevent the toxicity of Pd-NMs to the microbial community. Therefore, in addition to a single toxicity test, microbial metabolism and microbial community composition should also be assessed in the toxicological investigation of Pd-NMs on the actual microbial community, so as to understand the toxic effects of Pd-NMs on the microbial community from the perspective of molecular mechanisms.

Conclusions and perspectives

The widespread applications of Pd-NMs lead to their close contact with the ecological environment and their diffusion into the atmosphere, soil, water, and sediments. Subsequently, they migrate and transform in the environment and/or in the organism, and eventually cause harm to the organism. Much progress has been made in the investigation of Pd-NMs release, absorption, transport, and risk assessment in animal models, contaminated soil–plant systems, and microbial communities (Table 1).[21,28,29,87,100,103,110,116,123,125,130,148–158] However, research progress in the toxicology of Pd-NMs lags far behind their production rate, and also the lack of uniform criteria and guidelines for evaluating research projects and outcomes in this field. Also, the unique nature of Pd-NMs as new materials has led to many problems in evaluating the toxicology of these Pd-NMs. All these problems could lead to conflicts and hinder the development of emerging nanomaterials.

These Pd-NMs may affect the ecosystem function, exert cytotoxic and pro-inflammatory effects *in vitro*, and induce early changes in different target organs in *in vivo* model tests. Further studies are needed to more comprehensively and deeply characterize the physicochemical properties of Pd-NMs to explain in detail the complex interaction between their intrinsic characteristics and their toxic effects. Also, the nano-size of Pd-NMs makes it difficult to track them in the environment, so it is necessary to exploit a more accurate method to detect trace amounts of Pd-NMs in the environment. These problems should be analyzed by a systematic approach that involves the use of new high-precision equipment or new technologies and the characterization of Pd-NMs by multi-technique joint analysis.

Most *in vitro* studies have reported that Pd-NMs induce severe cytotoxic effects and dysfunction in different animal and human cells (Table 1). *In vitro* studies are helpful to understand the toxic molecular mechanism of Pd-NMs. However, current data on the toxicity of Pd-NMs *in vitro* are insufficient to reach a unified conclusion on the mechanisms, such as oxidative stress response, apoptotic pathways, cell cycle disorders, and DNA damage. In addition, the physicochemical properties, organic ligands, and surfactant interference with the toxicological properties of the Pd-NMs should also be considered. Therefore, it is necessary to further investigate the properties of Pd-NMs and the effects of their complex interactions between cell growth mediators on different toxic patterns. As an example,

Table 1 The toxicity of Pd-NMs to organisms

Pd-NMs	Investigated model	Findings	Ref.
Toxicity to animals			
$Pd(OH)_2$	Simulated lung fluids	Formed in the respiratory tract, and were toxic and allergic to humans and other organisms	103
$PdCl_2$ solution	Zebrafish embryos	Inhibited the survival rate and hatchability; leading to pericardial edema and cardiac malformation; inhibited the heartbeat rate; induced the maladjustment of stress-related genes	100
Pd/magnetite HNMs	Human skin (HaCaT) cell lines; human colon (CaCo-2) cell lines; rainbow trout gills (RTgill-W1) cell line	Did not trigger the production of ROS; did not affect the viability of selected mammalian and fish cell lines	28
ZnO/Pd HNMs	Human skin cells	ZnO/Pd NPs were more photocytotoxic than ZnO NPs on the viability of human skin fibroblasts	148
PdO/Co_3O_4 HNMs	BEAS-2B cells; RAW 264.7 cells; mouse lung	Superoxide production, glutathione depletion, cytokine production, and hierarchical cellular responses involving cytotoxicity in epithelial and macrophage lines; acute pro-inflammatory effects for mouse lung	149
Pd NPs	Human primary bronchial epithelial cells (PBEC); human alveolar carcinoma cell line (A549)	Absorbed by cells in PBEC; reduce the response of PBEC to the pro-inflammatory cytokine TNF-R	87
Pd NPs	Female Wistar rats	Caused significant tubular dysfunction of female Wistar rats; significantly altered the epithelial cells of proximal and distal renal tubules with varying degrees of severity	116
Pd NPs	Intact and damaged human skin in Franz cell	Permeated the skin in an *in vitro* system; a potential long-term effect inside the skin	29
Pd NPs	Human ovarian cancer cells (SKOV3)	Caused a decrease in cell activity and proliferation ability; caused the increase of cytotoxicity when the concentration increased; induced SKOV3 cell apoptosis by inducing mitochondrial dysfunction	150
Pd NSs	Tumor-bearing mice	No obvious hepatic toxicity by blood biochemistry assay; no detectable organ (spleen, kidney, liver, heart, and lung) damage by hematoxylin and eosin-stained imaging	110
Pd NSs	Female Balb/c mice	Slight lipid accumulation in the liver; led to spleen inflammation	158
Pd NSs	ICR mice	Accumulated in the liver, spleen, tumor, and kidney; cleared faster in the oral administration group	151
Phytotoxicity			
Pd element	Barley	Caused stress to the leaves at a low nutrient concentration	125
Pd NPs	Kiwifruit pollen	Changed the morphology of kiwifruit pollen; led to the rapid loss of endogenous calcium in pollen, resulting in the damage of the pollen plasma membrane	123
Pd NPs	*Sinapis alba*	The largest amount was found in leaves, followed by stems and roots	21
HNT-Pd	*Raphanus sativus* L.	Increased the number of aberrations in low-vigor seeds	152
Damage to microorganisms			
Pd solution	*Littorina littorea*	Diet is the most important carrier of Pd accumulation for *Littorina littorea*	153
Pd(II)	*Pantoea* sp. IMH	Induced the expression of anti-stress protein; induced detoxification of glutathione	154
Pd NPs	*T. thermophila*	Accumulated extensively in the food vacuoles of *T. thermophila*	155
Pd NPs	*V. fischeri*	Increased the biodiversity of *V. fischeri*; no adverse effect on the overall structure of *V. fischeri*	130
Pd NPs	*Candida albicans* ATCC10231; *Aspergillus niger*	Caused cell wall damage and oxidative stress	156
Pd element	*Caenorhabditis elegans*	Affected the growth ability of nematodes and had an effect on their reproductive ability	157

NPs: nanoparticles; HNT: halloysite nanotube; SP-ICP-MS: single particle inductively coupled plasma mass spectrometry; HNMs: hybrid NMs; NPs: nanoparticles; NSs: nanosheets; IL-8: interleukin-8; PGE2: prostaglandin E2.; ISO 11348-3: International Organization for Standardization; ROS: reactive oxygen species; DCFH2-DA: 2′,7′ dichlorodihydro-fluoresceindiacetate.

differences in particle intake and culture conditions in cell models simulating upper and lower respiratory tract environments can interfere with the toxicological characteristics of Pd-NMs.[87] Faced with this situation, it is necessary to establish more complex *in vitro* models to obtain more comprehensive data and to help infer actual *in vivo* pathological characteristics.

In vivo experiments have shown that exposure to palladium-based nanomaterials affects multiple organ systems, including the endocrine system and kidney system (Table 1). However, the toxicokinetic behavior, and changes in short-term biological indicators (cytokines, hormone serum concentrations, and urine protein content, *etc.*) reported in these reports, remains to be explained as well as whether they are stable at low doses and under long-term exposure conditions. From this perspective, Pd-NMs have a long-term and complex interaction with biological systems in the *in vivo* environment. Meanwhile, the toxicological characteristics of Pd-NMs may be related to the exposure patterns, differences in individual immune systems, and concentrations in biological media. Future investigations should focus on the toxicological effects of Pd-NMs on animals under low-dose, long-term exposure conditions (in practice, some workers may be exposed to low-dose Pd-NMs for a long period of time).

Many studies have focused on the biological hazards of nanoscale risk assessment, but few have studied the current and future concentrations and distribution of Pd-NMs in the environment. This requires a multidisciplinary team effort involving experts in materials, molecular biology, environmental toxicology, and physical chemistry. Also, innovative experimental methods and protocols are needed to guide the assessment of the full-cycle ecotoxicity of Pd-NMs. Furthermore, quantitative measurement of the concentration level of Pd-NMs in the real environment is strongly encouraged. Considering the lack of standardized testing procedures, the diversity of exposure pathways, and the differences in toxicity tolerance among individuals, there are still many difficulties in the environmental monitoring of Pd-NMs in the actual environment. Therefore, biological monitoring can be carried out at the same time, focusing on the investigation of biomarkers that mark physiological toxicity exposed in the real environment.

In summary, effectively defining the risk from the release of Pd-NMs, and the use of multidisciplinary methods to provide guidance are beneficial. Both would help to protect the health and safety of the ecological environment, and would be conducive to clarify the toxicity of Pd-NMs, thus contributing to paving the way for the development and application of sustainable nanomaterials.

Conflicts of interest

The authors declare no conflicts of interest.

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