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ECOTOXICITY OF CERIOUS NANOPARTICLES IN DIFFERENT ORGANISMS: A REVIEW[1]

ECOTOXICIDADE DE NANOPARTÍCULAS DE CÉRIO EM DIFERENTES ORGANISMOS: UMA REVISÃO

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ABSTRACT

Cerium oxide nanoparticles (CeO_2-NPs) are widely utilized in several areas such as; engineering, energy and biomedicine due to the redox properties ($Ce^{+3,+4,+5}$) indicating a reducing potential to oxidative stress in organisms. Thus, conflicting articles on the ecotoxicity of CeO_2-NPs have been published in recent years, demonstrating a protective effect of oxidation on organisms. To analyze and investigate the possible reasons, a comprehensive study of CeO_2-NPs with several variables and aquatic, terrestrial and flyers organisms was realized. Also, CeO_2-NPs did not demonstrate a ecotoxicity against organisms (aquatic, terrestrial, and flyers) compared to the current permitted legislation. At the same time, microorganisms such as algae (*Chlamydomonas reinhardtii* and *Pseudokirchneriella subcapitata*) showed an inhibitory effect on growth, possibly due to the redox properties of CeO_2-NPs causing an imbalance of reactive oxygen species in the solutions. Moreover, factors and parameters that affect the ecotoxicity of CeO_2-NPs are denoted, such as; concentration, exposure time, organisms, solution pH and properties (surface area and positive or negative charge). It is assumed that CeO_2-NPs more used and investigated and analyzed in aquatic, terrestrial and flyers environments using different organisms and comparing them, as well as using tracking methods to understand and study ecotoxicity processes involving metallic nanoparticles and organisms.

Keywords: Acute toxicity, cerium nanoparticles, *Chironomus riparius*, *Danio rerio*, *Pseudokirchneriella subcapitata*.

RESUMO

Nanopartículas de oxido de cério (CeO_2-NPs) são amplamente utilizados em diversas áreas como, engenharia, energia e biomedicina devido principalmente as propriedades redox ($Ce^{+3,+4,+5}$) indicando um potencial redutor ao estresse oxidativo nos organismos. Deste modo, artigos conflitantes sobre a ecotoxicidade das CeO_2-NPs foram publicados nos últimos anos, demostrando o efeito protetor da oxidação nos organismos e elevada toxicidade. Para analisar e investigar os possíveis mecanismos/razões da ecotoxicidade foi realizado um estudo abrangente das CeO_2-NPs com diversas variáveis e organismos aquáticos, terrestres e voadores. Assim, as CeO_2-NPs não demonstraram uma ecotoxicidade contra organismos (aquáticos, terrestre e voadores) comparados com a legislação atual permitida. Paralelamente, em micro-organismos como algas (Chlamydomonas reinhardtii e Pseudoirchneriella subcapitata) apresentam um efeito inibitório do crescimento possivelmente devido às propriedades redox das CeO_2-NPs ocasionando um desequilíbrio de espécies reativas de oxigênio nas soluções. Além disso, são denotados fatores e parâmetros que afetam a ecotoxicidades das CeO_2-NPs como; concentração, tempo de exposição, organismos, pH da solução e propriedades (área de

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superfície e carga positiva ou negativa). Presume-se que as CeO_2-NPs serão mais utilizadas e investigadas e analisadas em ambientes aquáticos, terrestres e voadores utilizando diferentes organismos e comparando-os, como também, utilizando formas de rastreamento para entender e estudar os processos de ecotoxicidade envolvendo nanopartículas metálicas e organismos.

Palavras-chave: *Toxicidade aguda, nanopartículas de cério, Chironomus riparius, Danio rerio, Pseudokirchneriella subcapitata.*

INTRODUCTION

The area of nanoscience and nanotechnology has been increasing and developing rapidly over the years; thus, the production and emission of nanomaterial into the environment tends to increase dramatically, leading to concerns about the possible potential for adverse impacts (MOORE, 2006; SUN *et al*., 2014). Moreover, the nanoparticles of cerium oxide (CeO_2-NPs), silver (Ag-NPs), and titanium (TiO_2-NPs) are highlighted, which are priority nanoparticles for evaluation in terrestrial and aquatic ecosystems at environmentally relevant concentrations (OECD, 2010).

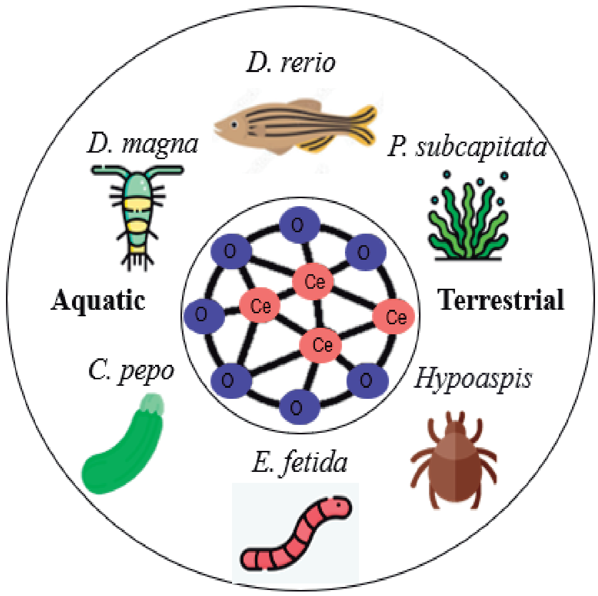
CeO_2-NPs are very utilized (production around 10,000 metric t per year) (MAJUMDAR *et al*., 2014), due to their redox properties allowing an easy transition between the Ce^{3+} and Ce^{+4} states vacancies on the surface of the CeO_2-NPs caused by crystal lattices providing reaction sites for other chemical elements acting as a product of reactive oxygen species (AUFFAN *et al*., 2014; CIOFANI *et al*., 2014) varying with intracellular pH (WASON *et al*., 2013). Furthermore, CeO_2-NPs demonstrate neuroprotective properties constituting a promising treatment for cancer (COLON *et al*., 2010) and wound healing (DAS *et al*., 2007; CHIGURUPATI *et al*., 2013). However, the great tendency of CeO_2-NPs to agglomerate in water is a major challenge in their investigation of ecotoxicity against microorganisms (LEE *et al*., 2013).

Parallelly, cerium oxides are used for several applications due to their optical properties such as; fuel additives (decrease CO_2 emissions); in woods and cosmetics (UV protection), catalytic filters (reduce exhaust particulate emissions from diesel combustion), and nanocatalysts (degradation of stable organic pollutants) (JUNG; KITTELSON; ZACHARIAH, 2005; PARK *et al*., 2007; SELVAN; ANAND; DAYAKUMAR, 2009; ZHOLOBAK *et al*., 2011; DAS *et al*., 2012).

Ecotoxicity of CeO_2-NPs is related to different characteristics such as; (a) discard; (b) physicochemical properties (size, shape, surface chemistry); and (c) environmental conditions (pH, ionic strength, colloids, and organic matter) (VAN-HOECKE *et al*., 2011; BOOTH *et al*., 2013). Moreover, in aqueous environments, CeO_2-NPs can undergo a variety of modification processes such as; sedimentation, heteroaggregation, and dissolution causing a significant effect on toxicity (ADEGBOYEGA *et al*., 2012; BAALOUSHA *et al*., 2013; LOUIE; TILTON; LOWRY, 2013). It is worth mentioning that in natural waters the main mechanisms that affect ecotoxicity are colloids and sedimentation normally caused for steric or electrostatic repulsion of cerium charges and pH of the medium (WANG; KELLER; CLARK, 2011; QUIK *et al*., 2012).

Ecotoxicity tests are dependent on the microorganism used, such as aquatic (bacteria, algae, zooplankton, mussels, and fish) and terrestrial (earthworms, oligochaetes, and plants) species (GARCÍA *et al*., 2011; COUTRIS *et al*., 2012; RÖHDER *et al*., 2014; TORRE-ROCHE *et al*., 2018) showed in Figure 1. It is worth mentioning that the most used organisms are the crustaceans *D. magna* and the zebra fish *D. rerio*, which are international accepted models for indication of acute toxicity and bioaccumulation in nanostructured products (SHARMA, 2009).

Figure 1 - Types of microorganisms used in ecotoxicity tests.



Source: Author's construction.

In this context, the present work aims to present a bibliographic review of the ecotoxicity of cerium nanoparticles, highlighting the microorganisms used and the results. Thus, the research was realized on *ScienceDirect* (https://www.sciencedirect.com/) and *Scopus* platforms. (https://www.scopus.com) from 2017 to Sep 2022. The novelty the work is to present the various CeO_2-NPs compared with the ecotoxicity results of microorganisms different.

METHODOLOGY

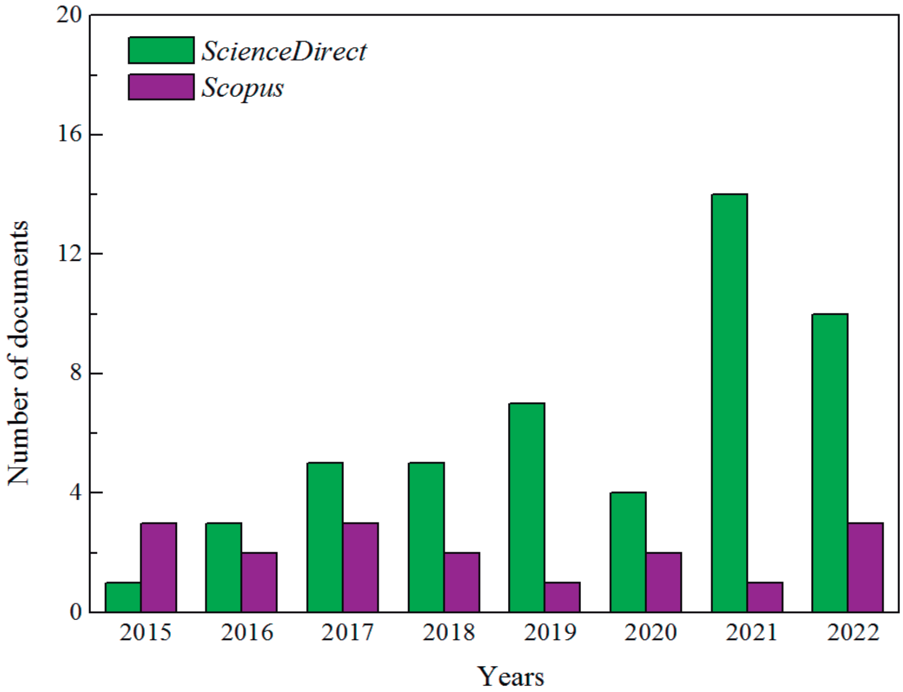
This work was characterized through a bibliographic review; the accomplishment consisted of the analysis of scientific articles on the *ScienceDirect* (https://www.sciencedirect.com) and *Scopus* (https://www.scopus.com) platforms, following the logic boolean, from 2017 to September 2022, demonstrating the ecotoxicity of cerium nanomaterial's that were studied through various microorganisms. Moreover, the following words were used for the search: ecotoxicity and cerium dioxide nanoparticles.

All the studies analyzed were those that presented the theme described and in association with ecotoxicity processes, aiming to analyze the main mechanisms and parameters that directly affect the toxicity in microorganisms for CeO_2-NPs.

RESULTS AND DISCUSSIONS

Figure 2 presents the articles found on the platforms *Science Direct* and *Scopus* from 2017 to September 2022.

Figure 2 - Published papers by year in the *Science Direct* and *Scopus* databases.



Source: Author's construction.

According to Figure 2, 49 and 17 articles were found in the *ScienceDirect* and *Scopus* databases, respectively. Briefly, the topic ecotoxicity in CeO_2-NPs demonstrates a growing trend of published articles correlating different sizes, shapes and applications, possibly due to new research involving energetic, optical, antitumor and bacterial applications and alternative models of ecotoxicity. Moreover, the increase in the number of articles occurs on both platforms with the first articles published in 2015, showed an increase of articles in percentage on *ScienceDirect* of 1400%, denoting a current, important and relevant theme. It is worth mentioning that the differences found in the databases may be due to the number of journals associated with *Scopus* and *ScienceDirect*.

Table 1 presents the tests/results found for ecotoxicity in cerium nanoparticles on *ScienceDirect* and *Scopus* platforms (2015-2022).

Table 1 - Tests/results found for ecotoxicity in CeO_2-NPs on *ScienceDirect* and *Scopus* platforms (2015-2022).

Nanoparticles	Methodological aspects	Concentration ($mg\ L^{-1}$)	Properties (particle size)	Results	Reference
CeO_2-NPs	Adverse effects utilizing a multimarker approach on the amphipods *Gammarus roeseli* and the bivalve *Dreissena polymorpha* (72 h)	0.01-0.1	8 nm	CeO_2-NPs accumulated in *G. roeseli*, causing a decrease in the size of the lysosomal system and the lipid peroxidation in the digestive glands	GARAUD *et al*., 2015
Carbohydrate--coated CeO_2-NPs	Investigation of acute toxicity and bioaccumulation in *Vibrio fischeri*, *Daphnia magna,* and *Danio rerio* (96 h)	100-400	8-13 nm	All concentrations of CeO_2-NPs there was no mortality for the microorganisms tested	MILENKOVIĆ *et al*., 2021
Poly (acrylic acid) -stabilised (PAA) CeO_2-NPs	Investigation of acute toxicity and bioaccumulation in freshwater microalgae *P. subcapitata* (72 h)	0.001-1000	84 nm	CeO_2-NPs in the ranges (0.001-1 and 700-1000) showed growth inhibition effect (± 50%) and biomass production	BOOTH *et al*., 2015
Small citrate--coated spheres (CeO_2-NPs)	Investigation of acute toxicity in diatoms *Nitzschia palea*, sediment-dwelling invertebrate *Chironomus riparius*, amphibian larvae *Xenopus laevis* and *Pleurodeles waltl* (96 h)	0.1-100	(2-5, 20-60) nm	All concentrations of CeO_2-NPs there was no mortality for the microorganisms tested	BOUR *et al*., 2015
CeO_2-NPs	Investigation of the uptake and excretion kinetics in the earthworm *Eisenia fétida* (28 days)	0.42	50-105 nm	CeO_2-NPs had no significant effect on growth	CARBONE *et al*., 2016
CeO_2-NPs	Evaluated the uptake and translocation of CeO_2-NPs for soybean plants (*Glycine max L. Merrill*) (10 days)	303	41.4 nm	$Ce^{+3, +4}$ ions were detected in the epidermis and cortex of soybean roots, but did not harm plant development	RODRIGUES *et al*., 2021
CeO_2-NPs	Examine the sublethal effects on the morphological features of the *C. riparius* (96 h)	2.5-2500	25 nm	High concentrations of CeO_2-NPs (>2000 $mg\ L^{-1}$), it presented deformed jaws (around 3.64%) and mentums (around 1.45%).	SAVIĆ-ZDRAVKOVIĆ *et al*., 2021
CeO_2-NPs	Influence of pH, natural organic matter and ionic strength for the alga *Pseudokirchneriella subcapitata* (48 h)	4.7-395.8	14 nm	CeO_2-NPs, pH (<6.6 low toxicity) and (>7.5 high toxicity)	VAN-HOECKE *et al*., 2016
CeO_2-NPs	Investigation of acute toxicity and bioaccumulation in *C. reinhardtii* and *Phaeodactylum tricornutum* (72 h)	0.1-200	9 nm	CeO_2-NPs showed no effect for *P. tricornutum*, however, for *C. reinhardtii* it presented a hormetic effect	SENDRA *et al*., 2018
CeO_2-NPs@CuO	Investigation of acute toxicity and bioaccumulation in *D. magna* and *D. rerio* (48 h)	1-500	8.2 nm	CeO_2-NPs did not showed toxic effects against the microorganisms tested, but mixed oxides CuO-CeO_2 induced some sublethal effects in fish.	JEMEC *et al*., 2015
CeO_2-NPs	Investigation of acute toxicity and bioaccumulation in *Oncorhynchus mykiss* in different organs/tissues (gills, liver and kidney) (96 h)	0.25-25	50 nm	CeO_2-NPs in high concentrations (>20) caused alterations in the gills, liver, and kidney of *O. mykiss*	CORREIA *et al*., 2020

Source: Author's construction.

In freshwater mussels, *G. roeseli* and *D. polymorpha*, strong interactions of CeO_2-NPs were not observed at concentrations of 10 μg L^{-1}. However, at high concentrations (>50 μg L^{-1}), there were high concentrations of hemolymph ions, indicating an activation in the protection mechanism of the mussels, it is worth mentioning that the tests were realized in a short time (92 h) (CANESI *et al*., 2012). Furthermore, the multi-biomarker approach allowed us to identify and evaluate the effects of CeO_2-NPs in mussels relating to lysosomal compartment, antioxidant defenses, and hemolymph ion concentrations enabling a better understanding of the ecotoxicity mechanism (SRODA; COSSU-LEGUILLE, 2011; GARAUD *et al*., 2015).

The production of CO_2 and O_2 in aquatic environments can cause changes in the system leading to a lack of energy in the organisms, inhibiting them. Thus, the bioaccumulation of CeO_2-NPs in *V. fischeri* and *D. rerio*, there were no significant changes in the production of CO_2 and O_2. However, *D. magna* showed an increase in CO_2 production, possibly due to the greater turbidity of the aqueous suspensions, directly affecting the respiration of the microcrustacean (LONCAREVIC *et al*., 2019). Furthermore, the carbohydrate coating on CeO_2-NPs does not affect the acute toxicity against the tested microorganisms (MILENKOVIĆ *et al*., 2021).

Ecotoxicity of PAA(CeO_2-NPs) against the microalgae *P. subcapitata* showed a growth inhibition effect, possibly due to the Kelvin effect (with the increase in temperature it increases the reactivity of chemical reactions) and synergism of the properties (surface area, particle size (10-60 nm) and superficial charge) demonstrating a higher solubility/dissolution kinetics, being able to saturate the solution with Ce^{+3} and Ce^{+4} (MANIER *et al*., 2013). Furthermore, stabilization with PAA does not contribute to the ecotoxicity of CeO_2-NPs, suggesting stabilization with other polymers (BOOTH *et al*., 2015).

The ecotoxicity of small citrate-coated spheres (CeO_2-NPs) observed appears to be highly dependent on the species tested due to several factors such as; exposure routes, organisms' defense systems, sensitivities inherent, and feeding behavior (VERNEUIL *et al*., 2014). It is worth mentioning that microorganisms produce external protective substances such as phytochelatins (diatoms) and mucus (chironomides) (BACCHETTA *et al*., 2012). However, the absence of amphibian protection may explain the toxicity found at high concentrations (BOUR *et al*., 2015).

CeO_2-NPs had no significant effect on the growth of *E. fetida*, however, for bioaccumulation, traces of Ce^{+3} were found within the tissues of the worms, supporting a low risk (TOURINHO *et al*., 2015). It is worth mentioning that CeO_2-NPs are affected for loaded soil surfaces such as; clay particles and organic matter can form complexes or co-precipitate natural nanoparticles, modifying the bioavailability (COUTRIS; JONER; OUGHTON, 2012; CARBONE *et al*., 2016).

Regarding plant uptake (*Glycine max L. Merrill*), the concentration of CeO_2-NPs in the aerial remained constant as a function of time due to the same proportion of biomass uptake for $Ce^{+3,+4}$ ions, indicating the transport of mass for water flow from plant leaves (GIESE *et al*., 2018). Furthermore,

CeO_2-NPs agglomerated in plant leaves with an average size of 25 nm were identified, suggesting an ecotoxicity effect due to the entry of ions into the plant's plasma layer (RODRIGUES *et al*., 2021).

Sublethal changes presented in chironomids (*C. riparius*) exposed to CeO_2-NPs are significant at high concentrations causing changes in metabolism, diet, and behavior (CVETKOVIĆ *et al*., 2020). It is worth mentioning, that at extremely high concentrations (> 2000 mg L^{-1}) of CeO_2-NPs, chironomids present a sudden elongation of all teeth, possibly due to the particle size facilitating the entry of ions and bioaccumulation processes (agglomeration) (SAVIĆ-ZDRAVKOVIĆ *et al*., 2021).

The pH, natural organic matter, and ionic strength parameters of the solution containing CeO_2-NPs in *P. subcapitata* showed significant values only for pH due to the effect of charge modification in basic and acid pH (protonation and deprotonation, facilitating entry into the seaweed's plasma membranes) (LI *et al*., 2010). It is noteworthy that more stable CeO_2-NPs suspensions demonstrate lower toxicity. Furthermore, the concentration of CeO_2-NPs was similar to ecotoxicity assays on algae suggesting that tests on algae may indicate a result of high toxicity against CeO_2-NPs (VAN-HOECKE *et al*., 2016).

The cell growth of *C. reinhardtii* and *Nannochloris atomus* increased at all concentrations tested, with a hormetic effect (dose-response phenomenon characterized by low-dose stimulation and high-dose inhibition), however, no growth effect was presented for *P. tricornutum* (SENDRA *et al*., 2017a). Therefore, some hypotheses may describe this behavior as; CeO_2-NPs can play a protective role in marine algae due to the $Ce^{+3,+4}$ charge ratio present on the NPs surface favoring the formation of oxygen vacancies (through band gap energy) causing a mimetic behavior similar to oxidative enzymes enabling the reuse of oxygen by algae through through mitochondria (CELARDO *et al*., 2011; SENDRA *et al*., 2018).

Nanocomposite of CeO_2-NPs with CuO did not show high toxicity significant against *D. magna* and *D. rerio*, but, the Cu^{+2} ions showed a slight deformation in fish, generally due to the physicochemical properties of the nanomaterial such as; surface area and surface charge (increase the reactivity of CeO2-NPs facilitating entry into the membranes of organisms) (VAN-HOECKE *et al*., 2009). However, in aqueous solutions the nanoparticles tend to form aggregates or agglomerates making it difficult to explain the toxic effect of the nanocomposite on *D. rerio* (AUFFAN *et al*., 2009). It is worth mentioning that the toxic effects on microorganisms are dependent on several factors such as the type of organism tested and the concentration of NPs used (JEMEC *et al*., 2015).

CeO_2-NPs in high concentrations (>20 mg L^{-1}) caused several changes in *O. mykiss* such as; liver (pyknotic nucleus, leukocyte infiltration and sinusoid enlargement), kidney (glomeruli retraction, nuclear hypertrophy and tubular degeneration), gills (aneurysms, lamellar hypertrophy and hyperplasia, epithelial elevation and congestion) possibly due to the CeO_2-NP redox properties relating the different oxidation states $Ce^{+3,+4,+5}$ under environmental conditions causing an increase in reactive oxygen production in the cell, mainly H_2O_2 (XIA; ZHAO; LU, 2013; COLLIN *et al*., 2014; CORREIA *et al*., 2020).

Therefore, CeO_2-NPs did not show ecotoxicity against different organisms (water, terrestrial and flying). However, they demonstrated a growth inhibitory effect on algae such as *C. reinhardtii* and *P. subcapitata* possibly due to the redox properties of CeO_2-NPs causing an increase in reactive oxygen species. It is worth mentioning that the ecotoxicity of nanoparticles is related to several factors such as; concentration, exposure time, organisms tested, solution pH and properties (surface area and positive or negative charge). Furthermore, the trend is that CeO_2-NPs will be increasingly investigated and analyzed in aquatic and terrestrial environments using different organisms and comparing them.

CONCLUSION

This review presented the types of organisms (aquatic, terrestrial and flying) utilized in the investigation and analysis of the ecotoxicity of CeO_2-NPs. Thus, the redox properties of CeO_2-NPs ($Ce^{+3,+4,+5}$) was the main mechanism of ecotoxicity resulting in higher production of oxygen causing the inhibition of al

gae growth and deformation of some terrestrial and aquatic organisms. It is worth mentioning that the properties of CeO_2-NPs are related to particle size, surface area and charge (positive or negative). Moreover, the main organisms used were zebrafish (*D. rerio*), alga (*P. subcapitata*), crustacean (*D. magna*), insect (*C. riparius*) and earthworm (*E. fétida*) demonstrating that each organism has a defense system and how it will be related with CeO_2-NPs. Also, several influential parameters on ecotoxicity were identified, such as; pH of the medium, concentration of NPs and organic material in the solution.

FUTURE PERSPECTIVES

It is assumed that CeO_2-NPs are more used in several applications, always seeking to improve the physical-chemical, biological, optical, electronic and mechanical properties. Furhtermore, investigation and analysis of further ecotoxicity studies are important and relevant, as most trials are 96 h, requiring trials of a wide range of time and use of a variety of organisms. Although, only a few aquatic and terrestrial ecotoxicity studies have been published so far of CeO_2-NPs most denoted to investigate acute toxicity. However, a multimarker approach would facilitate the screening and understanding of the ecotoxicity of CeO_2-NPs in aquatic and terrestrial environments.

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AUTHOR CONTRIBUTION

Druzian, D.M.: conceptualization, data curation, formal analysis, investigation, validation, writing-original draft, writing-review and editing; **Oviedo, L.R.:** conceptualization, validation, Data curation, writing-review and editing; **Loureiro, S.N.:** conceptualization, validation, Data curation, writing-review and editing; **Da Silva, W.L.:** conceptualization, data curation, formal analysis, investigation, validation, writing-original draft, writing-review and editing.

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