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Review

The potential exposure and hazards of zirconia nanoparticles: A review

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Abstract

Zirconia is upon nanoparticles widely used in various fields due to its adequate properties, making it an inherent element in nanotechnology. The enhanced expansion of their usage is not harmonized at the same level with toxicological investigations, and little interest has been given to their potential toxicity. Some studies considered using zirconia nanoparticles as a biomedical material as safe, while others considered them unsafe and harmful for living organisms; indeed, toxicity mechanisms involving reactive oxygen species production were reported. Such ambiguous points refer to the critical need for more related studies. The contradictions in the published works require a detailed review to understand the toxicity aspects and mechanisms of ZrO_2 NPs, including their implications associated with human and environmental exposure. This review aims to summarize mainly all published studies on Zirconia and its potentials harmful effects on living organisms; and likewise contributes to the accession of knowledge and a better understanding of the subject.

Keywords: Zirconia nanoparticles – Proprieties – Exposure- Hazards – Toxicology

INTRODUCTION

In recent years, nanotechnology has become one of the most important and exciting forefront fields in Physics, Chemistry, Engineering, and Biology. It shows a great promise for providing us, soon, with many innovations that will change the direction of technological advances in a wide range of applications, the unique proprieties that nanoparticles possesses including small size, optical proprieties and large surface area have clearly incited their usage in multiple scientific area such as medicine, environment and biotechnology (Poole and Owens, 2003 ; Wu and Tang, 2018). Nanotechnology deals with various matter structures having dimensions in the order of a billionth.

Nanomaterials or nanoparticles (NPs) are gaining significance in technological applications due to their tunable chemical, physical, and mechanical properties and enhanced performance when compared with their bulkier counterparts. They show potential for several applications including water treatment plants, oil refineries, petrochemical industries, industrial processes, catalytic processes, buildings and building materials, diagnostics, and drug delivery (Saleh, 2020). There are several methods for producing NPs, including condensation, attrition, chemical precipitation,

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ion implantation, pyrolysis, and hydrothermal synthesis (Pokropivny and Skorokhod, 2007).

Zirconia has been one of the most important ceramic materials for a century since 1975 (Garvie *et al*., 1975; Piconi *et al.,* 2003), it is incorporated into new high-performance applications ranging from bearing and wear to biomedical applications. Zirconia is a crystalline zirconium dioxide. Its mechanical properties are very similar to those of metals and its color is similar to the color of teeth (Piconi and Maccauro, 1999).

It is used in biomedicine as a biomaterial. The first proposal of the use of zirconium oxide for medical purposes was made in 1969 and concerned orthopedic application. ZrO_2 was proposed as a new material for hip head replacement instead of titanium or alumina prostheses (Chevalier, 2006) wear resistance and friction. In the research field of dentistry, the use of ZrO_2 in dental restoration applications has been a practice since 1998 due to its very high strength for load bearing as dental crowns, fixed partial dentures (FPDs) and dental implants. (Glauser *et al*., 2004)

Despite the exponentially grown applications of ZrO_2 nanoparticles, they could be toxic, and even if their toxicity is thought to be moderate, it may occur especially via chronic exposure as several studies indicated (Bartter, 1991; Shaw and Handy, 2011; Arefian *et al.,* 2015). The same advantageous properties of nanoparticles could also make them harmful and promote hazardous effects in living organisms, besides their low biodegradability, their small size, and others characteristics could facilitate their penetration in cells and tissues which consequently induce biochemical alterations in humans and animals (Dekkers *et al.,* 2017).

Some studies admitted that usage of zirconia nanoparticles as a biomedical material is safe while others regarded their uses as potentially risky and more investigations are needed (Sollazzo *et al.,* 2007; Buesen *et al*., 2014; Almjasheva *et al*., 2017; Ye and Shi, 2018; Han *et al*., 2020). Although mechanisms of zirconium dioxide toxicity are still poorly elicited and mostly unexplored, some studies have hypothesized that it can induce oxidative stress by enhancing reactive oxygen species (ROS) production in cells. Several adverse effects could be induced in living organisms which clearly refer to the clinical needs of investigate the potential hazardous effects of those particles (Zapór *et al*., 2015; Mishra *et al*., 2017). Recently it has been reported that ZrO_2-NPs can be used as an antitumoral agent, indeed, zirconia was described to induce tumoral HeLa cell death, through autophagy pathways and mitochondrial apoptosis mediated by ROS's production. This suggests that some biomedical usage of such nanoparticles can pass through ROS generation (Shang *et al*., 2021). On the other hand, antiviral activity of ZrO_2 Nps on H5N1 influenza virus was described in mice, it was indicated that zirconia efficiently protected mice against the extremely pathogenic H5N1 virus by disgracing viral load and suppressing the inflammatory via improving innate immunity and raising cytokines liberation in mice and their uses were rated as safe (Huo *et al*., 2020). By considering the previously mentioned data, their importance, and also the lack of studies on this subject also in order to clarify the actual state of the art on zirconia nanoparticles and their potential toxic effects, their safety or not ; this article will summarize all works and knowledge published on zirconium dioxide by highlighting its properties and its toxicity at different ranges; this review is the first of its kind which deals with zirconia Nps and their potential toxic effects aim to contribute and achieve a better understanding of all aspects of this topic.

1 Basic characteristics of zirconia nanoparticles

Zirconium or zircon (Zr) is considered as a transition metal with the atomic number 40. The term zirconium is an Arabic name derived from the word Zargon which means golden in color (El-Ghany *et al.,* 2016). Zircon is a gray-white element which usually doesn't occur as a pure metal in nature. However, it can be found as a free oxide called zirconia (ZrO_2) (Saridag *et al.,* 2013). The zirconium dioxide (ZrO_2) has been accidentally discovered in 1789 by the German scientist Martin Klaproth (Maziero *et al*., 2011).

According to researchers, zirconia nanoparticles belong to nanomaterials. The interest in them has increased in the last decade due to their advantageous proprieties (Garnweitner *et al*., 2010). They are extracted from two main minerals: baddeleyite. (South Africa), and zirconia sands (Australia) (Probster *et al.,* 2013; Perks and Mudd, 2019).

1.1 Structures and proprieties of zirconia

Zirconia has gained much importance and queries in multiple fields and domains thanks to their great, helpful, and accommodating properties (Table 1) such as biocompatibility, high mechanical strength, fracture toughness, temperature, corrosion resistance, great optical and dielectric proprieties in high refraction index, low solubility in water, a lipophilic character, and good chemical stability (Reischmann *et al.,* 1995; Kovalenko *et al.,* 2009; Bensaha and Bensouy, 2012; Aguilar, 2013; Durate *et al.,* 2017).

Table 1: Comparative proprieties of zirconia and others-based zirconia materials

Properties of Zirconia and based Zirconia materials				
Properties	Units	Zirconia (ZrO_2)	TZP	ZTA
Bending strength	MPa	>900	900–1200	>1000
Compression strength	MPa	1200 -5200	2000	2000
Young's modulus	GPa	210	210	350
Fracture toughness	Mpam_1/2	8	7–10	5.7
Maximum service temperature	K	1248-2522	11_10–6	12
Hardness	HV0.1	1250	1200	1975
Grain size	µm	≤ 0.5	<1 - <0.5	<1.5
Thermal conductivity	W m^{-1} K^{-1}	1.7 – 2.7	2	2

TZP: Tetragonal polycrystalline zirconia; **ZTA**: zirconia toughened alumina.

(Christel et al., 1989 ; Gautam et al ., 2016 ; Kurtz and Ong ., 2016 ; Huang et al., 2017; Irez et al., 2018)

Zirconia is a polymorph element that occurs in three phases under normal pressure depending basically on temperature: monocyclic (m), tetragonal (t), and cubic (c) form (Figure 1; Piconi and Maccauro, 1999). At ambient temperature and until ≈ 1170 ºC, zirconia is found in the monocyclic phase, between 1170 ºC and 2370 ºC in the tetragonal phase, and above 2370 ºC it transforms into the cubic form, with a melting point reached at 2680ºC. (Crawly, 2001; Tuan *et al.,* 2002; Mahiat, 2006; Harianawala *et al*., 2009; Lughi and Sergo, 2010). A volumetric diminution of nearly 3%– 10% resulting in residual stresses and cracking could occur during pure zirconia transformation from the tetragonal phase to the monocyclic phase as well volume increase, extended stresses, and cracks which might result from the cubic-tetragonal transformation due to cooling from the raised temperature (Terki *et al.*, 2006; Tanzi *et al.*, 2019). To minimize the risks concerning the occurrence of these dilemmas which could lead to catastrophic failure in zirconia-based materials, it is regular to stabilize this element by the addition of other oxides like cerium oxide (CeO_2), magnesia (MgO), yttria (Y_2O_3), and calcium oxide (CaO). This way the t-m transformations could be reduced and more stability of zirconia is reached (Grech and Antunes, 2019).

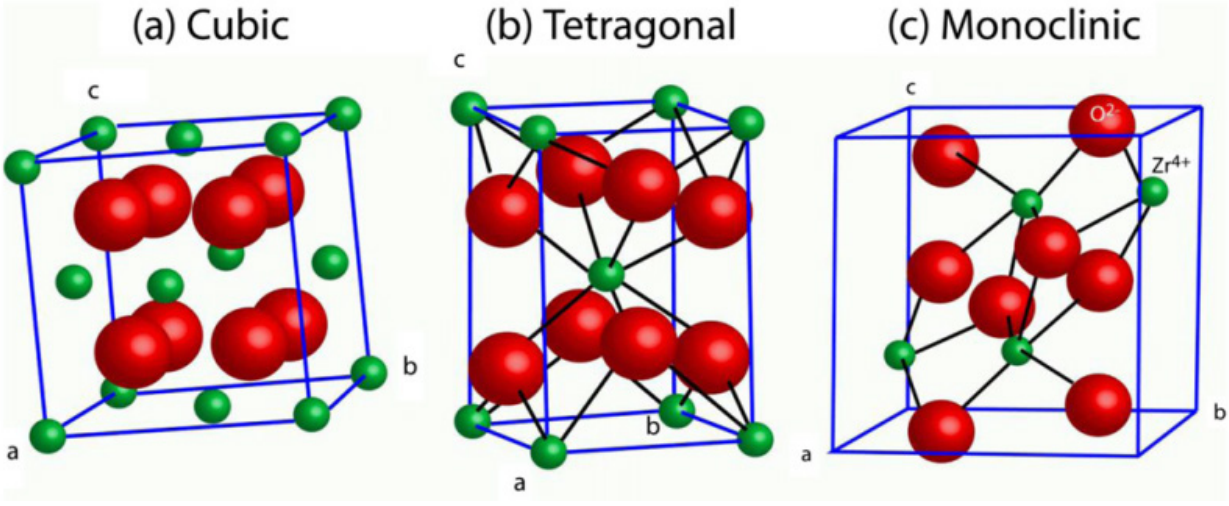

Fig. 1 Crystallographic phase change with the variation of temperature of the three ZrO_2 phases

The (c) zirconia form is a calcium fluorite model structure. At this phase, the zirconium ions occupy the highest points of the cube oxygen ions and located in the tetrahedral sites. (m) structure is illustrated in the P21/c space group, the atoms of the particles are sevenfold ordered with the O sublattice. As for the (t) form, the structure is presented by an elongated c-axis and can be considered as a slightly distorted version of the cubic form. Thus, it is called distorted calcium fluorite structure or even as a body-centered tetragonal (P42/nmc (137) space group) (Zhao and Vanderbilt, 2002; Chevalier and Gremillard, 2017).

1.2 Low-Temperature Degradation of Zirconia (LTD)

The big interest from the scientific community to zirconia, especially as a biomaterial, has grown consequently to the excellent proprieties that zirconium dioxide possesses, starting from the elastic modulus which is close to steel proprieties in addition to the mechanical proprieties that are superior to other ceramics materials, and the aesthetics appearances similarly to ceramics (Thamaraiselvi and Rajeswari, 2004; Thomas *et al.,* 2007; Kontonosoki *et al.,* 2019). However, an important issue has appeared in the uses of zirconia as a pure element or even as a biomaterial: the low-temperature degradation (LTD, Figure 2), also called hydrothermal aging of zirconium oxide. This phenomenon can affect the great capacities of the elements and seriously decrease their mechanical proprieties and resistance. The LTD has made the use of ZrO_2 as a pure element practically impossible and very risky, this has resulted in the innovation of the stabilized or partially stabilized zirconia (Durate *et al.*, 2016). The LTD is a process that occurs on the structures of zirconia materials with a sudden transformation from tetragonal (t) phase to monoclinic (m) phase, T-m transformation leads to an increase in the volume of zirconia crystals by +4 to 5 % which causes a stress in their structure. This stress could result in the generation of microcracks and fractures in zirconia-based materials (Praddo *et al.,* 2019). As a result of hydrothermal aging, all ZrO_2 biomaterials could be affected by mechanical failure and a decrease in their properties. The LTD is the principal problem for long term trustworthiness of all zirconia biomaterials, especially dental materials such as implants and also ZrO_2 orthopedics prostheses (Turon-vilas and Anglada, 2017). The microcracks and fractures generated by aging of zirconia *ie* t-m transformation can increase the water penetrations inside the structure which are involved in expanding cracks and deterioration of the zirconia ceramics and biomedical materials (Sivaraman *et al.*, 2017). Also, the aging of orthopedic zirconia prostheses can really affect wear performance with serious tissue damage and inflammatory reaction generated from the deformation of zirconia prostheses through inflammatory cytokines in the peri-prosthetic tissues (Patill *et al.*, 2020).

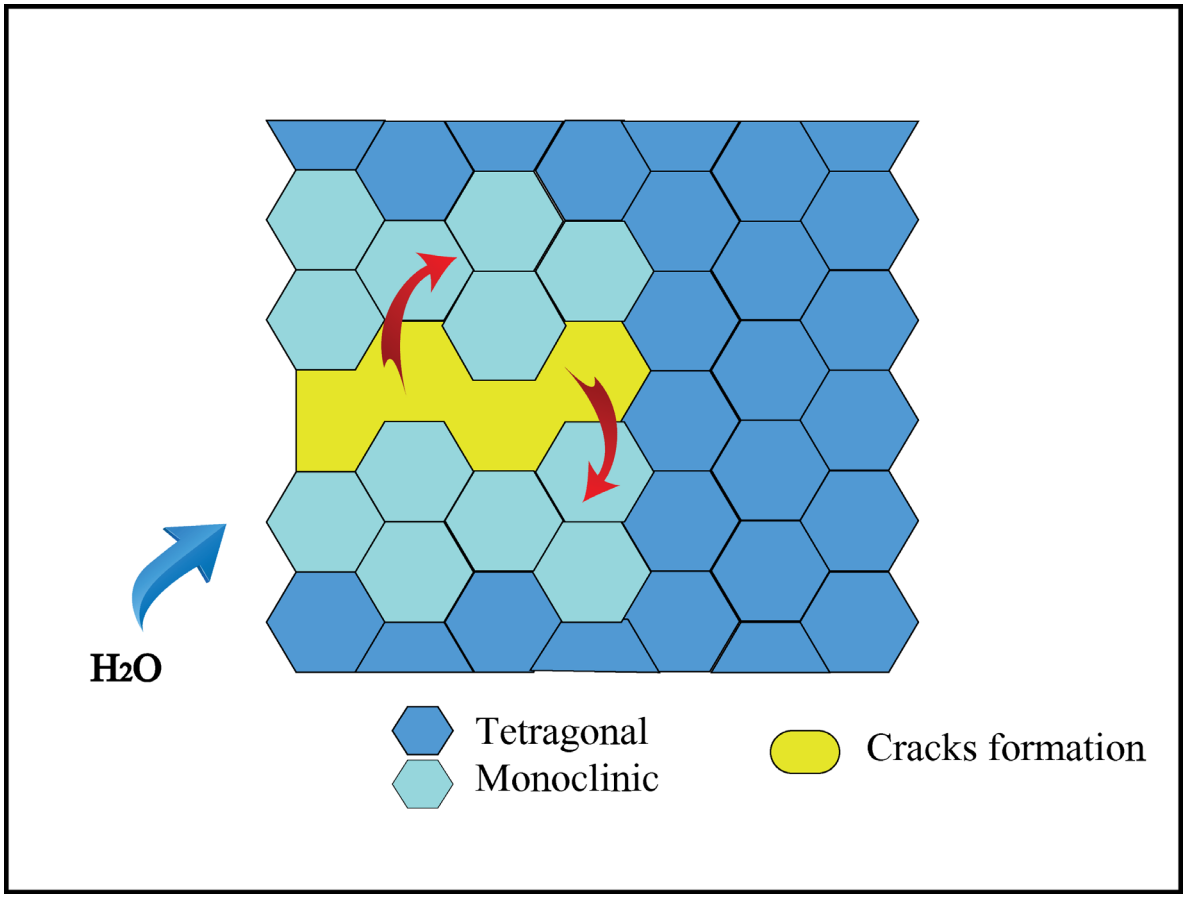

Fig. 2: Low température degradation ltd of zirconia.

Several factors could promote the aging of zirconia especially the contact of ZrO_2 based biomaterials with water and the wet environment of the human trap in the case of dental implants, crowns, and bridges, the constant mastication activity, and the oral PH. Many zirconia-based biomaterials have been retrieved from the market due to the aging issues as a result of their failure, many zirconia hip replacements (orthopedics implants) have been retrieved from the market in early 2000 (Soon *et al.*, 2017; Ramech *et al.*, 2020).

The low-temperature degradation (LTD) aspect has critically influenced academic dialogue on zirconia and its safety to use as a biomedical material. To prevent or try the limitation of those issues in the case of ZrO_2 biomaterials, a standardization from the International Standards Organization (ISO) has been realized: ISO 6872 (materials and ceramics for Dentistry), ISO 13356 (surgery implants), and Y-TZP (yttiria-stabilized tetragonal zirconia-based ceramics) (Gross *et al.*, 2020). Although some publications have proved that zirconia biomedical ceramics such as dental implants or even orthopedics prostheses that correspond to the ISO criteria could suffer failure, micro cracks, and surface degradation due to the hydrothermal aging. In 2001, the U.S food and drugs administration (FDA) confirmed that many orthopedics implants were retrieved from the market after some materials failure and fractures were observed (Chevalier *et al.,* 2007). On the other hand, Larsson *et al.* (2007) studied the strength and resistance capacities of four ceramic fixed partials denture (FDS) made from high rates of yttrium-tetragonal zirconia (Y-ZTP) fabricated by Procera® Zirconia, the clinical results showed several fractures in the connector area owing to defaults in the manufacturing of the materials, more precisely the connector's diameter. Lucas *et al.* (2014) interested to the impact of the low-temperature degradation with an accelerated artificially aging of Y-TZP (yttria-tetragonal zirconia crystals). Results proved that all Y-ZTP samples in whole aging conditions suffered from the t-m transformations at the surface of zirconia crystals.

Unfortunately, so far no method is effective in minimizing LTD, Koenig *et al.* (2021) studied 101 posterior dental elements, analyzing on each element surface: occlusal, axial, glazed, or unglazed. LTD developed in 3Y-TZP monolithic restorations 6 months after intraoral placement and progressed over time, they concluded that glazing cannot be considered as protection against ILD.

2 Source, application and pollution after use

The main known sources of zirconia are principally two minerals called baddeleyite and Zirconium silicate (zirconia sands). Zirconium element can be found mostly as an oxide in minerals containing potassium feldspar or plagioclase like gneiss, syenite, granite, and schists. Baddeleyite contains highs amounts of zirconium oxide and could also contain some others elements such as hafnium oxide although only at very small quantities. In fact, for getting zirconia, it is necessary to remove unwanted elements like silica, iron, and titanium from baddeleyite and Zirconium silicate (ZrO_2.SiO or zircon ore) (Blanchart, 2018). Zircon is widely abundant in Earth's crust with an average concentration 220 ppm, these minerals were found in many locations across the world such as Kavdor in Russia, Sao Paulo and Minases in Brazil and South Africa, where baddeleyite is contained in foskorite ore. In 1892, Joseph Baddeley was the first to discover the ZrO_2 mineral Baddeleyite in Sri Lanka in terrestrial rocks and also lunar rocks such as anorthosites, carbonatites, alkaline syenites, and kimberlites (Bayanova, 2006). The highest amounts of zirconia are contained in zircon favas, alteration product of an ore called eudialyte, with ZrO_2 concentration near to 97% while baddeleyite can contain 75% (Dill, 2010; Nielsen *et al.,* 2013; Anandan *et al.*, 2020). Since zirconia discovery, it has been used as pigments until its introduction in biomedicine as a biomaterial (Helmer and Driskel, 1969; Pilathadka *et al*., 2007; Gautam *et al.,* 2016).

2.1 Uses and applications of zirconia

Zirconia has been generating considerable interest in many industrial productions and applications thanks to its remarkable physicochemical proprieties (Guess *et al.*, 2012; Ghaemi *et al.,* 2017)**.** As a biomaterial, it has a wide range of applications such as the dielectric, electro-optic materials, electronic devices, gas sensors, as a pigment and refractory, and widely in ceramics industries (Rignanese *et al.*, 2001; Yu *et al.*, 2009; Seabra et Duran., 2015; Maslakah *et al.*, 2019).

The recent development in nanotechnologies has increased the uses of zirconia in the biomedical field especially in dental implants, bridges, and crowns as a result of its biocompatibility, low corrosion, and esthetical appearance. Three types of zirconia materials are used in the biomedical area: yttrium stabilized tetragonal zirconia (3Y-TZP), zirconia-toughened alumina (ZTA), and magnesium partially stabilized zirconia (Mg-PSZ) (Chen *et al*., 2016; Piconi and Maccauro, 2016; Naveau *et al.*, 2018; Nishihara *et al.,* 2019). Tetragonal zirconia is the most often used form due to its high mechanical strength (Denry and Kelly, 2008; Bona *et al.*, 2015; Ben-Nissan *et al.,* 2019). Zirconia dental implants have become better alternatives than others types of dental materials like titanium implants (He *et al.,* 2020). It is used in orthopedics as a femoral head for total hips replacement (Chevalier, 2006; Gherk *et al.*, 2019). However, the issue of low-temperature degradation (LTD) which causes deterioration of mechanical proprieties has made several controversial thoughts on the safety of its uses (Chevalier, 2006; Gherk *et al.,* 2019). Garvie *et al.* (1975) were the first to call zirconia materials "Ceramic steel". The first proposal for using this kind of biomaterials in orthopedics was presented in late sixties. Although in vitro studies on zirconia did not fully begin until the 1990s, it presents suitable characteristics and similar to stainless steel (Manicone *et al.*, 2007). It was used for the first time in orthopedic in 1986, in the USA and France. The focus of the initial biomaterials in this field was on magnesia partially stabilized zirconia (Mg-PSZ), yttria-stabilized tetragonal

zirconia polycrystals (Y-TZP) were a great alternative and a better substitute to Alumina biomaterials because of the higher fracture toughness and strength. At the beginning of the 1990s, zirconia materials owned the more beneficial mechanical properties amidst all the bulk oxides biomaterials (Affatato and Taddei, 2013).

Zirconia has also been used recently in the medical field as a nanocarrier in drugs targeting and delivery; such applications have been encouraged by the confirmed bioactivity of zirconia (Catauro *et al.,* 2008; Wang *et al.,* 2013; Nagy *et al.*, 2016). Zirconium compounds have been used in nephrology, too, for hemodialysis, hemofiltration, peritoneal dialysis, anti-cancer medicaments studies, deodorant and antiperspirant (Lee *et al.,* 2010; Hosseinzadeh *et al.,* 2019).

According to Piconi, (2001) more than 500 thousand zirconia orthopedics materials THR ball-heads had been produced at the beginning of its usage. However, it has been decreased, and replaced by mixed zirconia-alumina materials for hip and knee replacements (Piconi *et al.,* 2014).

2.2 Pollution after use

Nanoparticles released into the environment, deliberately or accidentally, disperse in the environment and reach water, soil and air. There, they can persist for a long time or be absorbed by biological organisms. They can act as an ecotoxicological risk, undergo biodegradation or bioaccumulate in the food chain (SCENIHR, 2006).

Extremely poor data can be found in the literature dealing with and discussing the environmental impacts and viable pollution of zirconia nanoparticles. Contamination of surface, groundwater, and soil by zirconium could happen in incidents at nuclear stations and atomic waste storehouses (Pechishcheva *et al.,* 2018). Among notable example is ^{93}Zr a radioactive zirconium isotope that possesses a high half-life which consequently could induce persistence and long duration pollution (Osvaath *et al.*, 2011). Even with the lack of studies on zirconia and their fate in the environment, it's unambiguous to admit that the massive increasing applications in various fields especially industrial could consequently intensify their concentrations in ecosystems. Although, the low mobility of zirconium compounds in soils they are persistent in rocks and soils (Fodor *et al*., 2010; Shahide *et al.*, 2013). Zirconia NPs synthesis processes could create harmful debris released in the environment (Viana da Silva *et al.,* 2019). Zirconium compounds may be transferred to aquatic ecosystems and interact with aquatic microorganisms thus accumulate and be translocate through the food-chain. Diminished toxicity was reported in micro-alga *S. capricornutum* and *Salmo gairdneri* Richardson fish and low environmental concerns were judged by Couture *et al.* (1989). On the other hand, the accumulation ability of Zr, compounds were described on cyanobacteria (Garnham *et al.,* 1991). Given the recent multiple thoughts for zirconia nanoparticles applications in remediation and decontamination of water from pollutants such as arsenic, reducing eutrophication and even reducing NOx engine emissions in the atmosphere which should encourage the evaluation of their environmental impacts. Also, nanomaterials may absorb deferent pollutants present in water surface leading to potential hazardous effects on aquatic organisms (Załęska and Doskocza, 2015; Drout *et al.,* 2019; Shao *et al.*, 2019; Rehman *et al.,* 2020). The inhalable crystalline compounds emitted by vehicles are a significant environmental health hazard, revealing the need for further investigation and assessment of zirconia levels generated by automobiles in urban areas worldwide Meza-Figueroa *et al.* (2021) described a CeO_2–ZrO_2 phase separation after sintering. This causes the emission of ZrO_2, CeO_2, and CeZrOx particles smaller than 1 μm, which can likely constitute a pollution source and could reach the alveolar macrophages in the lungs of living organisms.

3 Ecotoxicological effect in environment

3.1 Phytotoxicity

Zirconia phytotoxicity is generally considered as low. Very limited researches were conducted on this subject. Some data indicated that it can be absorbed by plants and accumulates there. In fact, it can be absorbed mainly by roots way despite its low phytoavailability and soil mobility. Otherwise, zirconium can cause a reduction in plants growth and alter their enzymes activity (Shahid *et al.,* 2013). However, other authors reported that, ZrO_2 has not induced any effect on maize seeds, and no phytotoxicity was observed, but it can be penetrated in seeds. (Karunakaran *et al.*, 2015)

In the same way, some plants growth-promoting rhizobacteria (PGPR) were exposed to TiO_2 and ZrO_2 nanoparticle suspensions (100 ml at 20mg/L concentrations). The titanium dioxide particles appeared to be highly toxic on PGPR compared to Zirconia nanoparticles (Karunakaran *et al.,* 2013). Similarly, ZrO_2-NPs had no significant effect on seeds germination of two plants: *Eruca sativa and Beta vulgaris*, so zirconia did not appear to be phytotoxic. ZrO_2 did not induce significant toxic effects on Wheat *Triticum aestivum* L, it was indicated that zirconia nanoparticles had a high uptake rate in wheat and a strong potential to accumulate in *Triticum aestivum* more than ceria oxide and titanium oxide NPs. Zirconia was found to have a high phyto-availability and its uptake could be done through the roots. (Zhang *et al.,* 2019)

3.2 Zootoxicity

This section summarizes studies evaluating the toxicity of zirconium dioxide in animals. Toxicological work on fauna is limited to the mouse, rat, or their cell line test. However, other biological models are less studied. Both *in vivo* and *in vitro* studies indicated that zirconia nanoparticles could induce

toxic effects when exposed to animal models. We must admit the poor number of the literature on zirconia toxicity and its mechanism or kinetics on living organisms.

Zleska and Doskocz (2015) investigated the ecotoxicity of the nano and micro zirconia particles on aquatic invertebrate crustaceans *Thamnocephalus platyurus, Daphnia magna*, and protozoans *Tetrahymena thermophila*. Zirconia nanoparticles appeared to be more toxic than the microform. The results obtained confirmed low impact of zirconia nano compounds in the acute toxicity test on *Thamnocephalus platyurus* and *Daphnia magna*. The values of the median effective concentration (EC_{50}) 24/48h were > 400 mg/L although ZrO_2 acute effects were harmful to crustaceans and protozoans according to the European Union criteria and slightly to moderate toxic under the US EPA criteria. In the chronic analyses, zirconia induced more toxic effects. The EC_{50} value of protozoa growth assay was 12.83 mg/L and 95.2 mg/L in the reproduction test of *D. magna. Besides, the* non-observed effects concentration (NOEC) was ≤ 0.19 mg/L, 0.78 mg/l respectively for *T. thermophila and D. magna.* The *T. thermophila* were most sensitive to zirconia nanoparticles exposure.

The embryotoxicity of ZrO_2-NPs was proved by Karthiga *et al.* (2018) on the embryos of zebrafish *Danio rerio.* The results showed that the ZrO_2-NPS induced severe effects on embryos development. Zirconia post-fertilization exposure induced a significant increase in embryos mortalities with a median lethal concentration (LC_{50}). 1µg NPs/ml. Zirconia caused significant severe hatching delay and developmental toxicity on *Danio rerio* embryos, in addition to multiple malformations such as ericardial edema, spinal curvature tail bent, axis bent, and yolk-sac; thus, embryos were powerless to hatch and died. Those results proved that zirconia nanoparticles could induce serious development toxicity.

Mishra *et al.* (2017) had studied the effect of ZrO_2-NPs on *drosophila melanogaster* via food. Zirconia caused delayed development of flies, behavioral disturbances which may be a neurological effect accompanied by a phenotypic change and intensive production of reactive oxygen species which may be the cause of the neurological effects reported. However, Demir *et al.* (2013), reported that zirconia did not have a genotoxicity effect on *drosophila melanogaster* with little doses.

A recent experiment conducted on the biological effect of hexagonal boron nitrite -zirconia composites in *drosophila melanogaster* have shown different degrees of effects. The exposition has been done by mixing Nanocomposites in insects' food, (10 % hBN 90% ZrO_2). The mixture had induced no significant effect on insect's development and a weak cytotoxicity. On the other hand, (90% hBN 10% ZrO_2) nanoparticles appeared to generate more cytotoxicity and phenotypic changes on *drosophila*. The author has considered the (10% hBN 90% ZrO_2) composite as safe to use in the biomedical field (Gautam *et al.,* 2019).

On the other hand, ZrO_2 had induced an inhibition of both bacteria and fungi (E. *coli, S. aruse, and Fusarium*) what proves its antibacterial and antifungal actions (Abdul Jalil *et al.*, 2017).

In contrast, some few *in vitro* studies considered that zirconia nanoparticles could be safe to use and had no toxic effect, or had a low toxic effect (Sollazzo *et al.*, 2007; Palmieri *et al.*, 2008; Ion *et al.,* 2010; Roualdes *et al.*, 2010; Almjasheva *et al.*, 2017).

4 Human risks

Only a few and limited publications on the impact of zirconia on humans can be found in the literature. Most previous works have been limited to only studying and reporting cases of zirconium compounds effect on workers. However, most of the previous publications do not confirm entirely that effects are caused by exposition to zirconium compounds (Kusaka *et al.*, 2001; Malczewska-Toht, 2001). On the other hand, zirconium compounds can induce dermal granulomas and pneumonitis (Nemery *et al.*, 1990)

Barrter *et al.* (1991) reported a case of a 62 years-old man that suffered from increased dyspnea. Even after he had stopped smoking for a long time, his pulmonary problem increased with time, this man had been exposed for a long time to zirconium compounds mainly composed of zirconia during 39 years of work in an optical company. Open lung biopsy showed advanced pulmonary fibrosis with extremely significant levels of zirconium particles variety, Barrter *et al.* (1991) judged to consider zirconium compound as a possible cause of pneumoconiosis and it should be investigated.

Another case of a 25 years-old nonsmoker woman was presented by Liippo *et al*. (1993). She worked for 3.5 years as a glazer of tiles in a ceramic factory where she had been exposed to zirconium silicate, this young woman has developed increased dyspnea; an open lung biopsy has been made and results revealed a decrease of lungs volume and fibrosis. According to results of biopsy, it was a hypersensitivity pneumonitis which was supposed to be caused by zirconium compounds inhalation.

Furthermore, Werfel *et al.* (1998) described a case of 51 years-old women who suffered for a long time from increasing pneumonia and dyspnea. She had been working for 19 years in a nuclear facility where she had been exposed to zirconium, iron, and tin; granulomatosis was revealed by radiography of the lung.

On the opposite, according to Marcus *et al. (1996),* a study carried on 178 workers exposed to zirconium compounds in north England has shown no evidence that zirconium exposition can cause pulmonary effects.

Zirconium compounds were also involved in allergic men's skin reactions. Shelley *et al.* (1958) indicated that several cases of skin granulomas were identified. These dermal allergic reactions were due to the usage of deodorants sticks containing zirconium particles. Williams *et al.* (1959**)** have reported two similar cases also but involving directly zirconium oxide or zirconia; dermal granulomatous was reported due to uses of lotions containing zirconia.

The focus of recent research has been on cytotoxicity of zirconia in human cells. During a study of ZrO_2, TiO_2, and AlO_3 toxicity on peripheral blood lymphocytes Demir *et al.* (2013) had demonstrated that zirconia does not induce any genotoxic effect neither cytotoxic effects. Although zirconia nanoparticles induced a decrease in phagocytosis ability, it increased oxidative stress on human macrophage as reported by Nkamgueu *et al.* (2000). Conversely zirconia particles did not decrease cell viability of macrophages, osteoblasts, and fibroblasts cells line although proliferation was decreased in a dose-dependent relation. Moreover, ZrO_2 particles did induce significantly an increased Il-8, Il-6 and Il-1B cytokines production in human macrophage. (Dallal *et al.,* 2013).

Lanone *et al.* (2009) indicated that zirconia has shown moderate toxicity in a comparative effect on alveolar epithelial and macrophage cell lines of 24 nanoparticles type. zirconia lC_{50} achieved by MTT assay, following 24 hours exposure on THP-1 cells, was approximated between those concentrations rang of the nanoparticles (171.9 (µg/ml) to 570.6 (µg/ml)). In a study carried out on the cytotoxicity of a novel colloid containing silica and zirconia (SiO_2@ZrO_2 Cryst) in human osteosarcoma (MG63), the MTT test has shown a significant cell viability decrease at 100 µg/ml. In the same way, DNA damage was detected by the comet assay; thus, EROS induction has increased at higher concentration of the colloids. According to the author, zirconia increased cytotoxicity and genotoxic effects were indicated (Di Virgilio *et al.*, 2014)

Zirconia may cause oral allergic sensitivity when present in the composition of dental implants, crowns, and bridges. Also, dermal effects and several cases were reported before (Sinițchi, 2017). However, zro2 nanoparticles are not considered as cancerogenic elements (Covacii *et al.*, 1999).

5 Toxic mechanisms

5.1 Toxicokinetic of zirconia nanoparticles

Exposure to nanoparticles could occur through four important ways including inhalation (respiratory tract), ingestion, dermal penetration, and the ocular way. Nanoparticles have structural characteristics and low size which could confer to them the special ability for penetrating upon biological tissues and accumulate there particularly in the respiratory tract of living organisms. Thus, the principal way of exposure to NPs is inhalation (Ameh *et al.,* 2019)**.** Some previous studies have reported many pulmonary effects due to zirconia and other zirconium compounds inhalation in occupational conditions. ZrO_2-NPs were also detected in the respiratory tract of the exposed cases what proves that they could accumulate in the lungs of humans and that this organ might be a target for this kind of particles (Barrter *et al.*, 1991; Liippo *et al.,* 1993; Werfel *et al.,* 1998). Besides, prior publications had reported cases of dermal effects and allergies caused by cosmetics products containing zirconium compounds. Thus, dermal way might also be a potential exposure way to this type of NPs (Shelley *et al.,* 1958; Williams *et al.*, 1959). On animals' model, it has been indicated by Sun *et al.* (2020) that zirconia nanoparticles could be accumulated in the liver of rats after intravenous exposure and induce oxidative stress. Some others studies have also reported the distribution and the retention of ZrO_2 NPs in the lungs, liver, spleen, heart, brain, and kidney of rats. This accumulation of zirconia can be certainly explained by their lipophilic character and their small size, they could make their way to the lung through lymphatic vessels and bloodstream. The liver might be the first target to ZrO_2 -NPs (Sun *et al.,* 2019; Yang *et al.,* 2019; Shang *et al.,* 2020). According to a recent study done on pregnant mice to determine whether or not zirconia nanoparticles have the capacity to cross multiple biological barriers after oral exposure, the results have indicated that the nanoparticles indeed had penetrated through the placenta and the fetal blood-brain barrier (BBB) and finally were able to reach and accumulate in the fetal brains. Moreover, the mechanisms implicated were receptor-mediated endocytosis and passing through para-cellular junctions in the maternal placenta and fetal BBB. The results demonstrate the accumulation potential of the zirconium oxide NPs (Wang *et al.,* 2020). In plants, some limited data in the literature have indicated that zirconia could be up taken by plants and seeds and accumulated in the roots. In wheat, it has been indicated that this type of nanoparticles had a high capacity to accumulate and uptake more than ceria oxide and titanium oxide NPs (Karunakaran *et al*., 2015; Zhang *et al.,* 2019)

5.2 Cytotoxicity of zirconia nanoparticles

Zapore *et al.* (2015) had put forward a very interesting hypothesis about the toxicity mechanisms of zirconium dioxide nanoparticles. It would seem that the ZrO_2 nanoparticles have a toxic potential through the induction of oxidative stress. During this study that was carried out on Chinese hamster ovary cell lines (CHO-9) and mouse testicular cells (15P-1) to evaluate the potential cytotoxicity of Nano ZrO_2, the results have indeed confirmed that the dose having generated an oxidative stress state was lower than the dose having shown a cytotoxic effect on the model cells. This was proved by measuring the oxidative and antioxidative cell state (TOS / TAS assay). The toxicity of these nanoparticles could be mediated by the production of ROSs. Similar results were obtained in a cytotoxicity study of ZrO_2-NPs. Exposure to different doses on 3T3 cell lines induced cell alterations, cell line was established from embryonic fibroblast cells primary mice, very similar to osteoblasts, a dose-dependent decrease in cell viability was observed. The zirconia nanoparticles also increased the production of ROS in lower doses than those estimated to be cytotoxic; this could indeed indicate that this

type of nanoparticles has a more or less significant oxidative stress generation power (Ye and Shi, 2018).

A decrease in glutathione peroxidase (GPx) activity was reported by Asadpour *et al.* (2014) after treatment with zirconium dioxide nanoparticles on PC12 and N2a cell lines derived from rat pheochromocytoma and mouse neuroblastoma. Cytological tests demonstrated that cell viability decreased after exposure to ZrO_2 due to the excessive production of ROS and the installation of a state of oxidative stress. Glutathione peroxidase (GPx) is a selenoprotein which has the role of eliminating EROS by the reduction of peroxides. It plays a vital role in the protection against oxidative stress and GPx and is considered as a secondary antioxidant line of defense. Any change in their activities may indicate the presence of oxidative stress (Valko *et al.,* 2005). Zirconia had induced a dose-dependent effects and an increased cytotoxicity on the cells lines that are explained mainly by the generation of reactive oxygen species (ROSs) (Asadpour *et al.*, 2014).

During a study conducted on the impact of several types of ZrO_2 nanoparticle having undergone surface modification (ZrO_2 APTS, ZrO_2 TODS, ZrO_2 PGA, ZrO_2 ACRYL) on alveolar macrophage cell lines (NR8383), several effects were observed. Nanoparticles generated dose-dependent cytotoxicity increased H_2O_2 radicals and increased the cytokines TNF expression. Then, the effect of the ZrO_2 ACRYL nanoparticles on the lungs of rats after intratracheal administration showed that the nanoparticles induced pulmonary effects, in particular more or less severe inflammations; so, it can be said that the nanoparticles of the Zirconium dioxide may be toxic for lungs as proved in previous studies on humans where several pulmonary effects related to zirconia exposure were indicated (Vennmann *et al.,* 2017).

Genotoxic effects considered to be probably linked to oxidative stress were noted in an evaluation of the cytotoxicity of certain zirconium oxide nanoparticles having received surface modifications. The toxicological test was carried out on cell lines of BALB / rats. Cytotoxic effects, in particular chromosomal alterations and morphological changes, were detected probably due to the inducing power of oxidative stress and the overproduction of ROS by ZrO_2. Furthermore, the cells viability assay MTT had shown that zirconia nanoparticles induced a cytotoxic effect only at high doses. Cell death and cell death indices were measured by Cytostasis (CBPI and RI) and had demonstrated a cytotoxic effect also at highest doses (Stoccoro *et al.*, 2016).

Prior research established by Asadpor *et al.* (2016) in order to conclude whether zirconia produces a significant toxic impact or not in rat cells PC12 and N2a reported that actually zirconia nanoparticles could induce important cytotoxicity at the dose range 31–2000 ug/ml. The cell viability assay (MTT) was performed to evaluate the impact of the nanoparticles on the cells and its significance level. The results had revealed dose-dependent increased cytotoxicity. As a consequence, several alterations could occur as a result of inflammation or pro-apoptotic cell signaling through caspase activation and cytochrome c release from mitochondria; accordingly, cellular damage could occur. Besides, the exposure of cells lines to zirconia had affected the levels of Reduced Glutathione (GSH) and caused its depletion. GSH plays an important role in the detoxification and the antioxidant system as a radical scavenger by supplying GSH to the antioxidant enzymes superoxide dismutase (SOD) and (GP_X); he changes in its activity could lead to serious alterations (Richard and Amstrong, 1998). An increase of lipidic peroxidation was also observed by the elevated levels of Malondialdehyde (MDA); enhanced levels of ROSs were also reported; DNA fragmentation and damage were indeed detected by the single-cell gel electrophoresis (SCGE). The results obtained by Asadpor et al. (2016) demonstrated that zirconia nanoparticles have a potential to induce oxidative stress which could lead to numerous toxic effects on living organisms.

The Genotoxic potential of zirconium oxide nanoparticles was investigated in a research paper set by Atalay *et al*. (2018). A fibroblast cell line derived from mouse L292 was exposed to various concentrations of a 20 nm ZrO_2 particles for 72 h. Following the exposition, multiple assays for identifying cells damages were performed. The Comet assay was performed to assess the genotoxicity and oxidative alterations by measuring two indexes which are the Genetic damage index and Damaged cell percent. Furthermore, Flow cytometry was used for evaluating the cells apoptosis. The results obtained proved that zirconia nanoparticles induced statistically significant genotoxic effects on L292. An increase in early apoptotic, late apoptotic, and necrotic cell counts was also indicated in a dose range from 50 μg/l to 150 μg/l. The authors concluded that the zirconia nanoparticles were able to induce a dose-dependent alteration in the cells lines and genotoxicity confirmed by the presence of a high similarity relation among the comet investigation and the flow cytometry parameters.

In a study investigating the toxicity *in vitro* of zirconia, alumina (Al_2O_3), and silica (SiO_2) nanoparticles on Wistar rat blood cells, Kozelskaya *et al.* (2016) reported diverse morphological changes on Red blood cells (RBCs), ZrO_2 NPs had induced an increase in the micro viscosity of the rats' erythrocytes at smaller concentrations than SiO_2-NPs. The atomic force microscopy (AFM) of the blood cells had shown that zirconia nanoparticles had caused morphological alterations; at high concentration, a destruction of the binocave form with structural cracks and erythrocyte swelling were observed. These effects were explained by the fact that ZrO_2-NPs formed protein-lipid crosslinks in the membranes of red blood cells which may be the result of the hydrophobic interaction. Kozelskaya *et al.* (2016) excluded the idea that the zirconia NPs could easily penetrate inside the cells with their agglomerates and size.

5.3 In Vivo Toxicity studies

It has been shown in the literature that the size of particles plays a very important role in their toxicity. Pizzoferrato *et al.* (1987; Table 2) had exposed mice by IP to several types of

metallic and non-metallic particles including the microparticles ZrO_2. Peritoneal Washing was carried out one week after injection. The analysis of the cell suspension showed that the zirconia microparticles decreased the levels of macrophages and polymorphonuclear leukocytes with a lower rate of phagocytosis than in the case of other particles which was explained as being probably due to the particles size considered large. The bulk of studies on the subject have reported that zirconia nanoforms are more toxic than the microform.

Superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT) are antioxidant defenses that play a major role in detoxification and especially in the elimination of free radicals produced by ROSs. Any upheaval or change in their activities can cause significant toxic effects in various organs, zirconium dioxide can induce the production of ROS and therefore cause a state of oxidative stress which can be explained by a disruption of the balance between the antioxidant defenses and the free radicals (Valko *et al.,* 2005). Olmedo *et al*. (2011) indicated that zirconium dioxide nanoparticles can be distributed to the liver and lungs of Wistar rats after (IP) intraperitoneal exposure. Levels of ZrO_2 were detected in blood serum, liver, and lungs. Decreases in the activity of superoxide dismutase (SOD) in the lungs and liver of rats have been described. However, an increase in the production of superoxide anion free radicals (O^-) in the alveolar macrophage has been observed. ZrO_2-NPs could induce oxidative stress in several organs, in particular the lungs. Thus, the accumulation and distribution of these types of particles depends essentially on their sizes.

After an exposure to ZrO_2 by intraperitoneal route in wistar rats, changes in the activity of oxidative stress biomarkers were observed in liver and kidneys in addition to a significant decrease in the activities of SOD, GPx, and CAT, and an increase in the levels of MDA with the serum levels of liver enzymes ALT, AST and ALP. Histological changes were also reported in addition to liver inflammations and kidney damages as congestion and destruction of the glomerular capsule space (Arefian *et al*., 2015).

A recent study conducted by Yang *et al.* (2019) on the toxicity of zirconia nanoparticles in Mice had reported distinct effects. After a single intravenous injection of deferent doses, histological changes were observed in the liver. Lymphocytic infiltration, micro granulation, degenerative necrosis of hepatocytes, and changes in antioxidants enzymes activity were also observed in the liver and serum of the ICR mice. Decreased levels of catalase (CAT) and superoxide dismutase (SOD), increased levels of lipidic peroxidation marker Malondialdehyde (MDA), and serum Alanine Aminotransferase (ALT) were observed. According to the author, zirconia induced oxidative stress and may be the cause of its toxic potential.

Another recent study proved that a sub-chronic I.V exposure to ZrO_2 in rats could induce significant hepatic effects, severe inflammation, hepasteatosis, and cell death by the induction of oxidative stress. An increase in reactive oxygen species (ROSs) production, a significant increase in Malondialdehyde (MDA) levels in the activity of aspartate aminotransferases (ASAT), alanine aminotransferases (ALAT) and a decrease in the activity of superoxide dismutase (SOD) have been detected. It has been indicated that zirconia had an accumulation potential in rat's livers and lungs after the IV injection and effect on the gene's expression.

Sun *et al.* (2020) reported the hepatic toxicity and the biodistribution of zirconium oxide nanoparticles *in vivo* and *in vitro*. Rats were injected by I.V with nano-zirconia of 38-nanometre size. The effects of ZrO_2 were observed in 28 days and rats were sacrificed at six periods point between day 1 and 28 with the objective of evaluating the progressive impact after the injection. The results obtained had indicated that high levels of ZrO_2 were accumulated in the liver during the 28 days, but their concentrations decreased from the day 10 post-injection. It had provoked a decrease in levels of SOD and increase in MDA, ALT, ASP, and a continuous release of cytokines: IL-1α, IL-1β, IL-6, IL-12, TNF-α. Some histological alterations were observed in addition to fatty degeneration of perinuclear halos of hepatocytes, cytoplasmic relaxation, edemas of hepatocytes and cellular apoptosis with a formation of autophagosomes. The RNA-Seq and RT-qPCR analysis has shown a modification of 68 genes expression in the liver.

Previous research papers and reviews had confirmed that mixture fibers usually containing zirconia nanoparticles called Refractories Ceramic Fibers (RCF) are highly toxic to the lungs when inhaled and could even be carcinogen. RCFs are synthetic fibers, also called vitreous fibers (SVFs) that can contain a mixture of many particles including Al_2O_3, SiO_2, and ZrO_2. In the late 1980's, the RCFs were in group 2B by the IARC (possibly carcinogenic to humans) (Maxim *et al.,* 2018). Prior studies conducted on 344 rats and Syrian golden hamster for assessing the chronic toxicity by RCFs inhalation containing mixtures of several nanoparticles including high purity zirconia confirmed that RCFs inhalation was highly toxic to the lungs; Fibrosis, bronchoalveolar, adenomas and carcinomas (Mast *et al.,* 1995; Mcconnell *et al.,* 1995).

Conversely, there are some studies which judged that ZrO_2 possess a very low toxicity level or even no toxicity. Bunsen *et al.* (2014) investigated the sub-acute toxicity of SiO_2, ZrO_2, and $BaSO_4$ nanoparticles on rats through the oral way. The rats were gavaged with high doses, 1000 mg/kg BW/day, during 28 days period. Results showed only an increase in the alanine aminotransferase (ALT) and a decrease in the prostate and testicles weight in zirconia groups.

Table 2 : *in vitro* studies performed with ZrO_2

Model	Exposure design	Exposure period	Doses	ZrO_2 Size	Major effects	Reference
Fibroblasts (10 $T_{1/2}$)	Cells cultured on zirconia disks	72h	Nd	1.5 mm , 5 mm disks diameter Particles size Nd	• No genotoxicity • No cytotoxicity	Covacci et al., 1999
Oestoblasts-like cell lines (MG-63)	Cells cultured on zirconia disks	24h	Nd	3 cm disks diameter particles size Nd	▪ miRNA genes ↑ regulation : • Skeletal genes: PMF1, SHOX, FGFR1, IGF1. • Bone formation genes: BMP1, AMBN. • Cartilage genes: NOG. ▪ ↓ regulation : • Skeletal genes: TRAPPC2.	Palmieri et al., 2008
Human lymphocytes	Direct exposure to ZrO_2	1 h	1 , 100 or 1000 µg/mL	Nd	• No DNA damage (comet assay). • No effects on cells viability .	Braz et al., 2008
Human macrophage (THP-1) and alveolar (A549) cell lines	Cells incubated with ZrO_2 and 23 different Nps	24h	0.1- 3300 µg/mL ZrO_2 and 23 different Nps	32 nm	• Effects on cells viability ZrO_2 LC_{50}: 171.9 µg/mL . • Moderate cytotoxicity for ZrO_2 (also Alumina and Ceria Nps). • Lower toxicity than CuO, Zn and Ti Nps.	Lanone et al., 2009
Human macrophage	Direct exposure by adding ZrO_2 or Al_2O_2 to cultured cells	7 days	30 mg (Powder)	80 - 175 µm	• ↓cell viability. • Alterations of cell membrane. • ↓intracellular potassium /sodium ratio. • ↓ phagocytic ability of cells. • Changes in Oxidative metabolism.	Nkamgueu et al., 2000

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(MG-63), (THP-1) and fibroblast cell lines	Direct exposure individually of cultured cell to ZrO_2 , cobalt-chromium-molybdenum (CoCrMo) or titanium (Ti)	48h	5:1, 10:1, 50:1, and 100:1 particle per cell.	> 0.3 µm	• ZrO_2 and Ti had No effects and CoCrMo ↓ cell viability. • ↑interleukin (IL)-6, IL-8 and tumor necrosis factor (TNF)-a. • All particles induced dose-dependent ↓ cell proliferation. • ZrO_2 ↑lactate dehydrogenase (LDH) in (MG-63). • ZrO_2 induced ↓ toxicity than CoCrMo.	Dalal et al., 2012
human kidney (HEK293) and peripheral blood lymphocytes cells	Cells incubated with TiO_2, ZrO_2, or Al_2O_3 NPs	Nd	1, 10, or 100 µg/ml	6 nm	• No DNA damage (comet assay), no genotoxicity reported. • No cytotoxicity .	Demir et al., 2013
Saccharomyces cerevisiae	Flasks containing the yeast were spiked with deferent concentrations of ZrO_2, Fe0, Fe_2O_3, Mn_2O_3 or TiO_2 Nps	10 h	100–1000 mg/l	20 - 30 nm	• High tendency of Nps including ZrO_2 aggregate in aqueous media. • ZrO_2 induced low toxicity. • Mn_2O_3 was toxic to Saccharomyces cerevisiae.	González et al., 2013
Rat (PC12) and Mouse (N2a) cell lines	Cells incubated with ZrO2 NPs	48h	0, 31, 62, 250, 1000 or 2000 µg/mL	100 nm	• Dose-dependent ↓ cells viability. • Cytotoxicity at concentrations above 15.6 µg / mL. • ↓GPX	Asadpour et al., 2014
(MG-63) cell lines	Cells incubated with colloidal silica spheres coated with zirconia SiO_2 & ZrO_2	24h	5, 10 , 50 , 100 µg/mL	782 - 891 nm	• ↓ cells viability. • ↑DNA damage (comet assay and Single Cell Gel Electrophoresis). • ↑ROS . • concentration-dependent↓ of GSH/GSSG ratio. • particles crossed cells membrane and detected in cytoplasm.	Di Virgilio et al., 2014
Mouse testicular Sertoli cells (15P-1) - Chinese hamster ovary cells (CHO-9)	Cells were exposed to ZrO_2 Nps	7 days	0 – 500 µg/mL	100 nm	• ↓ cells viability at 200-500 µg/ml • ↑ total oxidative status at lower doses than cytotoxic ones . • No DNA damage (comet assay). • ↓ cells proliferation.	Zapór et al., 2015

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(PC12) - (N2a) cell lines	Suspensions of ZrO_2 Nps were dispersed on cultured cells medium at various concentration	12h – 72h	31- 62 - 250 - 500 1000 or 2000 µg/mL	8 – 50 nm	• Dose-dependent↓ cells viability. • IC_{50} PC12: 66.68 - 53.32 and 40.82 µg/mL 12, 24, and 48 h exposure respectively. • IC_{50} N2a : 45.49, 33.06, and 26.27 µg/mL. • ↑ROS , ↑ MDA , ↓GSH . • ↑DNA damage (Single Cell Gel Electrophoresis).	Asadpour et al., 2016
mouse fibroblasts (Balb/3T3)	For cell transformation assay (CTA), Cytokinesis-block micronucleus cytome assay (CBMN) and Colony-forming efficiency assay(CFE) : Cultured cells were exposed to various concentrations of ZrO_2 or TiO_2 Nps (Uncoated and coated) for each assay .	24h-72h	(CFE) : 8.3–266.6 µg/ml (CTA): 91.6, 183.3 or 366.6 µg/ml, (CBMN) : 32, 64 or 128 µg/ml	Uncoated: 261 ± 79 nm Silicated: 276 ± 85 nm Low citrated: 83 ± 32 nm (After dispesrion in the medium)	• ZrO_2 and TiO_2 localized inside; outside cells as agglomerates /aggregates . • ZrO2 NP ↓ cell viability after 72h . coated induced no effects . • all ZrO_2 ↑ apoptotic and necrotic indices , ↑ cytotoxicity, Chromosomal • damage by ↑ micronuclei formation • all ZrO2 ↑ DNA damage (comet assay) at 24h and ↓ at 48 , 72 h. • ZrO2 ↑ morphological transformation. • ZrO2 capacity to ↑ cell death. • Uncoated ZrO2 showed higher toxicity than coated NPs.	Stoccoro et al., 2016
red blood cells (RBC) of Wistar rats	ZrO2, Al_2O_2 or SiO2 suspensions at various concentrations were mixed with (RBC) and incubated.	2-5 min	4 ng/ml - 2 mg/ml.	80-100 nm	• ZrO2 ↑micro viscosity of cells , ↑cracks on the surface of (RBC). • ZrO2 and Al_2O_2 induced Cells swelling resulting in total loss of the biconcave shape at 2 mg/ml. • ZrO2 Nps may pass through the cell membrane (not confirmed). • hydrophobic interaction ZrO2 NPs and cells ↑cracking ofthe swollen cells as a result of ↑rigidity. • SiO2 was less toxic .	Kozelskaya et al., 2016

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alveolar macrophages (NR8383)	Cells incubated with Four coated ZrO2 NPs at a concentrations range : aminopropylsilane (APTS), acidic tetraoxadecanoic acid (TODS), or acidic acrylic acid (Acryl).	16h	50 , 100 , 150 or 250 µg/mL	9 - 10 nm	• In culture medium ZrO2 NPs agglomerates and finally sedimented. • Accumulation of NPs in cells observed. • Cytotoxicity , dose-dependent effects on Cells and deteriorations at high doses . • ↑ TNFα ,↑ lytic enzyme glucuronidase , ↑ H_2O_2.	Vennemann et al., 2017
Mouse Fibroblast cell lines (L929)	Cells incubated with ZrO2 NPs at a concentrations range.	72 h	50, 100 or 150 µg/ml	20 nm	• Genotoxicity observed at all doses of ZrO2 NPs. • ↑DNA damage ,↑early apoptotic, late apoptotic, and necrotic cell counts (confirmed and correlated with flow cytometry and Comet assay). • ZrO2 capacity to induce apoptotic effects.	Atalay et al., 2018
Osteoblast-Like (3T3-E1) cell lines	Cells incubated with ZrO2 or TiO_2 NPs at a concentrations range.	24h – 48h	0, 10, 20, 40, 60, 80, 100, or 150 µg/mL	31.9 ± 1.9 nm	• ↓ cell viability , high cytotoxicity at 150 µg/mL for both NPs . • Biocompatible at lower doses. • ↑ ROS generation most important at 100 µg/mL , no generation at 10 µg/mL. • ↑ early apoptotic cells , late apoptotic and necrotic cells after 48h . • Concentration-dependent↑ apoptosis at >10 µg/mL. • Cell ;morphological changes at >10 µg/mL. • ↑ expression of osteogenesis-related genes >10 µg/mL.	Ye and Shi., 2018

Nd : not determined , TiO_2: Titanium dioxide , Al_2O_2: Alumina , SiO_2: Silica , Mn_2O_3: Manganese oxide , Fe_2O_2 : Iron (II) oxide , CuO : copper oxide .

6 Conclusions and recommendations for future research

Zirconia is one of the widely used biomaterials due to its unique properties. The various applications of ZrO_2 specifically as a biomedical material and in drug targeting had made critical not only the evaluation of its safety for public health but also its toxicity. Data from the current literature mainly indicated that it has a potential toxicity proven by several in vivo and in vitro studies, namely its bioaccumulation and the induction of oxidative stress. Given the importance of zirconia in nanotechnologies, the literature on its toxicity and potential danger can be considered poor and very limited compared to other NPs. This is a capital point to take as a concrete hope.

Both in vivo and in vitro toxicity probe of zirconia NPs exposed some difference in their results due to experimental designs and conditions (exposure concentrations, times, cell lines and deferens incubation times), and the difference of shape, size, and even charge of ZrO2 -NPs used. The evolution of nanotechnology had reinforced the fears on their potential negative impact on public health and on environment.

Due to the observed lack of investigations on zirconia nanoparticles impacts on the environment, their fate, their release pathways, sources and potential pollution hazards, a comprehensive view of the issue cannot be formed and as a prominent prospective the recommendation of new related studies and more extensive approaches on multiple biological models is judged to be greatly needed; indeed, understanding the bioaccumulation, biodistribution, toxicokinetic and potential genotoxicity of ZrO_2 NPs constitute an ideal way to evaluate their real potential toxicity , so, more specified and related investigations should be conducted such ways will hopefully allow a better exploration of the toxicity mechanisms of those nanoparticles. Some important aspects should be taken into consideration in the evaluation of zirconia namely their biocompatibility or not, their toxic effects after long time uptake, exposure and their ability to accumulate and penetrate biological barriers. A more specific understanding and detailed studies to judge the level of toxicity and the inherent mechanisms involved in the effects of zirconia NPs are considerably needed to ensure the improvement of safety guidelines and limit the risks of these particles.

This review can be seen as a slight contribution to expand the knowledge of ZrO_2-NPs and the dangers associated with exposure. To conclude, it is crucial to mention that the advantages of zirconia nanoparticles must be counterbalanced toward their possible toxic effects for preserving public health.

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