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CRITICAL REVIEW

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Insights on toxicity, safe handling and disposal of silica aerogels and amorphous nanoparticles

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Amorphous forms of silica have always raised a lot of interest by the scientific community and are nowadays rapidly growing in commercial applications. These are commercialized as aerogels or as nanoparticles, which can feature many similarities, not only in the synthesis process but also because clusters of nanoparticles are commonly released from aerogels. Nevertheless, the health effects of amorphous silica materials are not fully understood, as occurs with many other nanoforms. Amorphous silica is known to be less toxic than its crystalline form, but toxicity studies, regulatory aspects and handling practices are still scarce. In this work, the knowledge on toxicity of amorphous silica nanostructures and suitable regulations are reviewed. Furthermore, relevant safety practices for handling these materials are discussed and strategies used to recycle and dispose them are summarized.

Environmental significance

Currently, many nanoforms are used in commercial products and their research is widespread. However, there is a clear lack of knowledge on the health and environmental effects of such substances and, information on their handling and disposal is also frequently incomplete. In the current paper, we review, analyse, and discuss the toxicity, ecotoxicity, workplace exposure, handling practices and alternatives of disposal of silica aerogels and nanoparticles. These types of amorphous silica nanostructured materials are very common despite the lack of knowledge about their effects, safe handling and disposal. Based on the published literature, in our paper we conclude about the health effects and ecotoxicity of these nano silicas and present the best available information/recommendations regarding safe handling and disposal. No similar paper is published in the literature, consequently most of the information we present is fragmented in the open literature and not easily widespread. Our paper also contributes to a more informed and sustainable development of nanomaterials, in particular silica aerogels and amorphous silica nanoparticles in general.

Introduction

In 1930, Samuel Stephens Kistler developed a systematized procedure to produce a new material that he designated as "aerogel" (published in Nature in 1931[1]). This protocol, currently called supercritical drying, consisted in replacing the liquid (alcohol) inside the pores of a silica gel by a gas, with little or no shrinkage, which was accomplished by turning the solvent in a supercritical fluid, thus avoiding the

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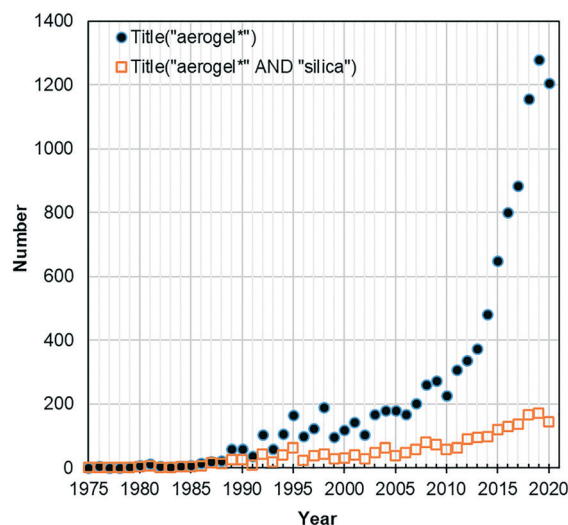
Fig. 1 Number of published works documented in Web of Science database with the terms "aerogel*" and "aerogel* AND silica" in the title (search date: 30-12-2020; incomplete data for 2020).

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capillary forces existent during evaporative drying. The work of Kistler continued with the application of the developed procedure to obtain thoria aerogel catalysts[2,3] and with the characterization of the structure and properties of the very new silica aerogel.[4–6] The thermal conductivity of the latter (*ca.* 15 mW m^{-1} K^{-1}) was since the beginning one of its most noticed features.

In the following decades, the works found on aerogels are very scarce (not many years have more than one article during that period), and only started to raise in the 1980s due to the increasing interest in the application of aerogels as Cherenkov counters and catalysts. The growth of works under this topic has been exponential since then (Fig. 1), which is certainly justified by the unpaired aerogel characteristics, *i.e.*, a fine nanostructured 3D network composed of clusters of interlinked nanoparticles, with porosity usually above 90% (mainly in the mesopores range), that results in a high surface area, ultra-lightweight solid.[7,8] The discovery of subcritical drying for aerogels was reported by Deshpande, Smith and Brinker in a patent (US5565142A) granted in 1996.[9] Since then, the logic behind the term "aerogel" has been expanded to many chemical systems, including numerous oxide and organic matrices, and also using alternative ways of drying by non-supercritical conditions, like freeze drying, evaporative drying at ambient pressure and under vacuum.[10–12]

The preparation of aerogels with subcritical drying conditions commonly involves silylation, a modification of surface chemistry to turn them hydrophobic, in order to avoid adhesion forces of the solvent molecules to the solid and allow the so-called spring-back effect during drying.[10] Thus, materials prepared in this way will usually feature the presence of methyl groups in their surface. Despite the drying process itself only impacts structural properties[10] (which already may reduce the surface area of a xerogel and, as consequence, can lead to less exposure of functional surface groups), the referred silylation process creates differences in xerogel and aerogel counterparts in terms of surface groups. These might lead to different toxicity of both counterparts. Nevertheless, silylation might be required for both aerogels and xerogels counterparts to avoid degradation by moisture and, thus, achieve the stability/durability required for the application.

The percentage of works related to silica aerogels (Fig. 1), the first ones to be synthesized, is still very significant even nowadays, with a contribution of *ca.* 15–20% of the total amount in the last decade; this is mostly due to their extremely low thermal conductivity, since they act as superinsulators.[13] They are also the ones better adapted so far for large-scale production and commercialization.[11,14,15] They are available in the form of neat silica monolithic panels, films and powder/granules,[11,15] but they normally need mechanical reinforcement in order to sustain handling and application loads,[16] thus they are often provided in the form of blankets (reinforced with a mat of fibres), boards (aerogel granules linked with an organic binder) and diverse

composites.[11,15,17–19] In 2016 the global aerogel market was estimated at 538.14 million USD.[20]

The Business Innovation Observatory of the European Commission has not ignored the potential of market growth of aerogels in the commissioned report of 2015 "Advanced Materials: Aerogels, getting their second wind (Case Study 56)".[21] The applications of silica aerogels are headed by their use for thermal insulation (oil and gas ducts and vessels, construction, packaging, equipment protection), but the surface/porosity-dependent applications are being extensively explored by the research community, namely the use of aerogels for adsorbents, catalysts, fillers, filters, sensors, energy storage, drug/cosmetics delivery, tissue engineering and medical implants, among others.[11,22–25]

Silica aerogels are identified as excellent material candidates for many biomedical and environmental applications, where toxicity and health concerns of these nanostructured materials should be considered.[23,24,26,27] However, the number of works in the literature related to their health effects, toxicity (for humans and other species), safe handling and disposal is very low. The scarce literature is mainly related to cytocompatibility/ biocompatibility of silica-containing hybrid aerogels and studies of life cycle assessment, and they will be presented in later sections of this review. Thus, the studies focused on the toxicity, safety and disposal of silica aerogels (and other aerogels) are urgent, considering the growing interest for aerogels and their potential applications. Still, we can use our knowledge to correlate the existing studies on silica nanostructures with silica aerogels. This correlation is set on the basis that silica aerogels have a pearl necklace structure of interlinked secondary silica particles, with tens of nanometres of diameter, and these particles or their clusters are the entities that generally detach from the aerogels and pose the most serious concerns.

When an aerogel is in contact with water, its surface is first wetted, and water progressively penetrates the aerogel pores. There are two mechanisms of aerogel particle shedding due to wetting. Some sorts of aerogels, *e.g.* silica, alumina and titania, erode in water and particles of 10–40 μm are released from the aerogel.[28] This erosion can be completed in 30 minutes in a stirred vessel.[28] On other hand, carbohydrate and protein aerogels swell in water forming a hydrogel-like matrix. This phenomenon is caused by the rearrangement of their backbone in contact with water leading to fast collapse of the pores.[28]

During the machining process of aerogels, particles are released into the air due to mechanical abrasion. This mechanism is very similar to the machining of standard materials (*e.g.* steel, concrete)[29] with one important difference – the released particles easily create an aerosol cloud in the vicinity of the machinery, due to the aerogel's very low density.[30] Aerosol cloud tends to stay in the air for much longer time than for standard materials (*e.g.* concrete dust).[31] In case of aerogel-based composites, aerogel particles are mostly attached to fragments of the matrix material what decreases the formation of the aerosol cloud.

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The target of the current article is to gather pertinent information about the safe handling procedures, disposal alternatives, and health and environmental impacts of silica aerogels and silica-composed alike nanomaterials, thus contributing to a more informed use of these materials. To the best of our knowledge, this kind of approach is novel in the literature, as existing review publications do not focus on so many aspects and usually only cover the synthesis/chemistry, toxicity for humans and seldom silica degradation and effects on the environment. Moreover, in a recent opinion paper, the clear lack of knowledge on environmental impacts and ecotoxicity of these nanomaterials was highlighted.[32]

Microstructural features of silica nanomaterials

The toxicity of nanoforms towards any form of organism, is related with aspects such as crystallinity, aggregation state and surface chemistry.[33,34] Solubility of the nanoform in a cell is influenced by those and reflects the ability of living creatures to eliminate these substances. Usually the dissolution of a nanoform implies its degradation and thus, the less soluble the nanoform the more toxic, in the long-term, it is.[35,36] Exposure to soluble nanoforms can cause acute toxicity.[36] For the case of silica, crystalline forms are significantly less soluble than amorphous forms, whose dissolution in water produces non-toxic products.[35,37,38]

In order to observe the degree of long-range order of the secondary silica particles in silica-based aerogels, we include the X-ray diffraction patterns (XRD) of some aerogels in Fig. 2: one non-organically modified (obtained from TEOS) and two organically modified (with methyl – MTMS – or vinyl – VTMS – g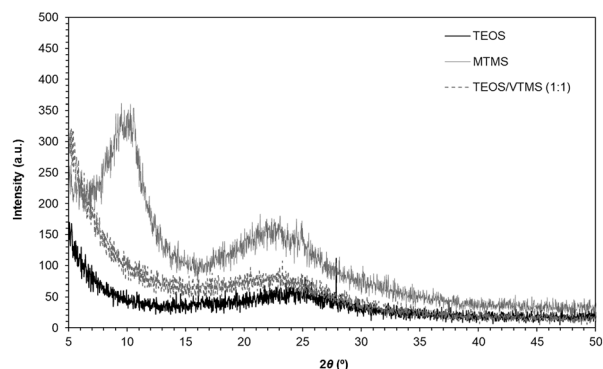roups). As can be seen, all the analysed aerogels show a completely amorphous nature and therefore, also will have their secondary particles. The broad hump observed at 22–23°, which slightly shifts to a lower angle with the amount of organosilane, is due to the spacing of silicon atoms and angle in the siloxane bonds (Si–O–Si).[39] In crystalline silica a sharp peak is observed in this region, which is not the case for the aerogels. The broad peak observed at lower angles, for example at *ca.* 10° for the MTMS aerogel, gives information about the spacing between Si atoms linked to alkyl groups (*i.e.* related to the channels created due to the presence of the organic pendant groups).[39] This peak was not seen (in the studied range) for the TEOS/VTMS hybrid aerogel, since its XRD pattern is more similar to that of TEOS aerogel. Probably, the vinyl groups are preferentially oriented towards out the silica matrix due to the high amount of TEOS in the hybrid aerogel,[40] or this peak may be shifted to a lower angle.

In the last decades, a fast growth in nanotechnology has taken place as a consequence of the advantages of using nanoparticles (NPs), including silica NPs, in a wide range of fields.[41,42] Consequently, the synthesis, handling and use of silica NPs represents an increasing risk for human health to be evaluated.[43,44] Apart from crystalline silica (CS), which is one of the main components in the Earth's crust (in the forms of α- and β-quartz, α-tridymite, α- and β-cristobalite, keatite, coesite, and stishovite), engineered or synthetic amorphous silica (SAS) nanoparticles are among the most produced NPs worldwide for construction materials, industrial and consumer products.[33,45,46] Depending on the method used for the synthesis – pyrogenic, precipitation, sol–gel – three different SAS nanomaterials are obtained, namely fumed silica, precipitated silica and colloidal silica.[45,46] Moreover, with the explosion of the nanomedicine field, mesoporous silica (MS) and organosilica NPs have also been largely synthetized and studied for drug delivery, imaging and biosensor applications due to their good biocompatibility and superior loading properties in comparison with the crystalline and amorphous silica.[47] SAS NPs are of utmost interest when searching for health or environmental effects of silica aerogels, for the herein described reasons. Thus, this survey includes the effects of this kind of NPs, whenever there is a lack of information regarding silica aerogels.

Ecotoxicity effects of silica nanomaterials

Silica nanoparticles and their agglomerates eventually end up in the environment. Some of their major uses are in paints, plastics, ceramics and car tires.[48,49] Al-Kattan[50] studied the release of amorphous silica NPs from paints using weathering experiments. Silica release from a silica-containing paint was 0.065 mg L^{-1} and the released silica consisted in large particles (32% smaller than 100 nm). When aged, the same paint released 20 mg L^{-1} of silica particles with only 10% smaller than 100 nm.

Fig. 2 XRD patterns of a tetraethyl orthosilicate (TEOS)-derived aerogel, a methyltrimethoxysilane (MTMS)-derived aerogel and a hybrid aerogel obtained from TEOS and vinyltrimethoxysilane (VTMS) (1:1 molar ratio), all silylated with hexamethyldisilazane (HMDZ) and submitted to ambient pressure drying. Analysis of the milled aerogels performed in a Philips diffractometer, model X'Pert, in θ–2θ Bragg–Brentano geometry, with accelerating voltage of 40 kV, a current intensity of 35 mA, a step of 0.025° and a time per step of 1 s. The used anticathode was Co-K$_{\alpha 1}$ 1.78897 Å, but the data was converted through the Bragg's law to Cu-based wavelength.

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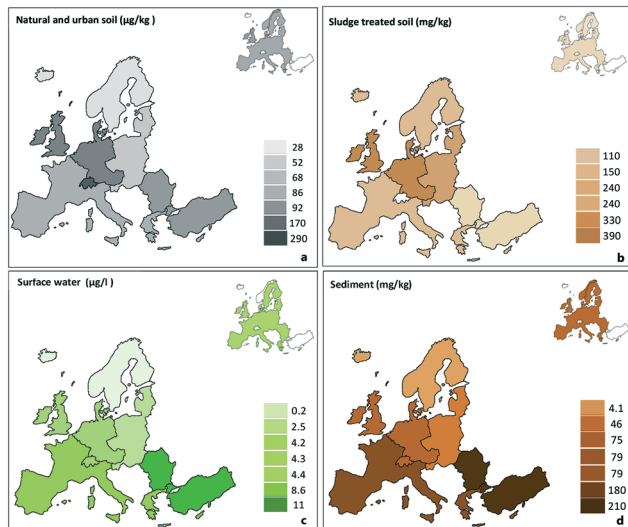*Environ. Sci.: Nano*, 2021, **8**, 1177–1195 | **1179**

Fig. 3 Distribution of nano silica in a) natural and urban soils, b) sludge treated soils, c) surface water and d) sediments in some regions of Europe in 2014. Reproduced from ref. 49 with permission from Elsevier, copyright 2018.

Some authors have investigated the presence of silica NPs in the environment.[48,49,51] In Europe, nanosized silica was found and quantified in surface waters, sediments, urban soils and effluents (Fig. 3). In average, the annual concentration increase of nano silica was 6.2 μg kg^{-1} in European soils, 6.3 mg kg^{-1} in sludge treated soils and 6.7 mg kg^{-1} in sediments.[48] Graca and co-authors[51] analysed the existence of nanomaterials in seawater collected from the Southern Baltic sea. The nanomaterials consisted of nanoparticles and nanofibers, mainly of silica but chrysotile was also found. The concentration of these nanomaterials was also seasonal-dependent and their origin was biogenic and geogenic.

Nanoparticles can disrupt the biota since they reach and accumulate in the lithosphere and hydrosphere. Thus, different ecotoxicity studies of amorphous silica nanoparticles found in the literature are reviewed in the following subsections. The effect concentration at 20% (EC$_{20}$) or 50% (EC$_{50}$), *i.e.* the concentrations of NPs leading to 20 or 50%, respectively, of the tested organisms affected by them, are common parameters to assess the toxicity of silica nanoparticles.

Phytotoxicity and effect on soil microorganisms

Silica has a beneficial effect in plants, and thus it is not phytotoxic. In fact, silica relieves biotic and abiotic stresses (metal toxicity, salinity, drought, temperature stress), acts as a physical barrier, reduces susceptibility to enzymatic degradation and enhances pathogen and pest resistance.[52,53] Silicon is shown to accumulate in the leaf tissues.[54] SAS NPs has the same beneficial effects as regular silica to plants.[54]

Slomberg *et al.*[55] studied the phytotoxicity of silica NPs of different sizes towards *Arabidopsis thaliana*. MT-ST (14 nm;

ORGANOSILICASOL), TEOS-derived 50 nm and TEOS-derived 200 nm particles were studied. When the seeds were grown in hydroponic solutions of nanoparticles without controlling the solution's pH, the plant's development was impaired and became yellowish. This result was attributed to the effect of the NPs on reducing nutrient availability by increasing pH, rather than to the NPs themselves. However, when the pH was controlled, plants grew similarly to blanks, and growth was even promoted in some cases, concluding that silica NPs are not toxic towards this plant up to concentrations of 1000 mg L^{-1}.

Clément *et al.* studied the phytotoxicity of silica NPs on *Linum usitatissimum* (flax) using germination tests.[56] Commercial non-modified 14 nm NPs (fumed silica), amine-modified NPs 22 nm (from the commercial particles), amine-modified NPs 292 nm, amine-modified NPs 448 nm (both obtained by Stöber process) and HASE-grafted NPs (hydrophobically modified alkali-soluble emulsion; modified with a macromonomer) were studied. Some phytotoxicity was observed with the NPs although it was not concentration dependent up to 100 mg L^{-1}. The phytotoxicity index for the different NPs was lower than that of the reference toxicant (potassium dichromate) and thus, it was concluded that silica nanoparticles, even with different functionalization, are not toxic towards flax.

The ecotoxicity of nano (amorphous, from sodium silicate) and bulk silica particles was studied toward plant growth-promoting rhizobacteria (*Bacillus megaterium*, *Azotobacter vinelandii*, *Pseudomonas fluorescens*, *Brevibacillus brevis*).[57] Silica had no toxicity towards these bacteria. In contrast, microbial viability increased in the presence of both types of silica, enhancing microbial populations, in water and saline media. In soil, silica also increased the bacterial populations and decreased soil pH, being not toxic at concentrations up to 1000 mg kg^{-1}. Similarly, Shah and Belozerova tested the influence of amine-functionalized silica NPs in the germination of lettuce seeds.[58] It was found that the high loading of silica onto the soil promoted an increase in the number of culturable soil bacteria and improved the growth of the lettuce seeds, increasing the shoot/root ratio.

Book and co-authors determined the EC$_{20}$ of different commercial Levasil colloidal silica nanoparticles (Na-stabilized, alumina modified and silane modified) towards soil bacteria *Pseudomonas putida*.[59] Silica was not toxic for these bacteria as the EC$_{20}$ was higher than the highest tested concentration (500 mg L^{-1}).

Ecotoxicity effect on marine organisms

The ecotoxicity effect of silica nanoparticles on marine organisms is compiled in Table 1. The toxicity of silica particles and NPs (commercial hydrophilic fumed (Aerosil), hydrophilic silica microparticles (Sipernat) and green fluorescent amorphous silica (Kisker Biotech)) towards the marine bacteria *Vibrio fischeri* was studied by Ríos and co-authors[60] and Casado *et al.*[61] According to the EC$_{20}$ and EC$_{50}$

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Table 1 EC_{20} or EC_{50} of silica nanoparticles on different marine organisms

Organism	Silica type	EC_{20} mg L^{-1}	EC_{50} mg L^{-1}
Vibrio fischeri[60]	Aerosil 380	2104	—
	Aerosil 200	1654	—
	Sipernat 50	2434	—
Vibrio fischeri[61]	50 nm NPs	—	>1000
	100 nm NPs	—	>1000
Paracentrotus lividus[62]	4–40 nm NPs	—	0.06 embryos/0.27 larvae
Phaeodactylum tricornutum[56]	NPs 14 nm	—	48.6
	Amine-modified NPs 22 nm	—	160
	Amine-modified NPs 292 nm	—	225
	Amine-modified NPs 448 nm	—	256
	HASE-grafted NPs	—	640

analysis (Table 1), silica NPs were not toxic regarding this bacterial strain. In fact, Ríos et al.[60] refer an inhibition percentage of only 10% in the studied range of concentrations and materials.

Gambardella et al. investigated the effect of silica NPs (Tal Materials Inc.) on the development of sea urchin Paracentrotus lividus.[62] After exposing sperm to SiO_2 NPs (4 to 40 nm, Tal Materials Inc.), the fertilizing ability did not seem to be affected by the particles. However, toxicity towards embryos and larvae was clearly observed (Table 1). Although the percentage of anomalous embryos did not change with the concentration of NPs, the percentage of developed embryos decreased with increasing NPs concentration. Likewise, the percentage of larvae with anomalies was concentration dependent. Staining studies revealed damages at the cellular level by fluorescence measures of cilia, stomach and perioral body in larvae exposed to low concentrations of NPs and in larvae derived from sperm exposed to the NPs (Fig. 4). Therefore, silica NPs are toxic towards this organism and affect its reproduction ability.

The silica NPs prepared by Clément et al.[56] were also evaluated with Phaeodactylum tricornutum, a marine diatom.
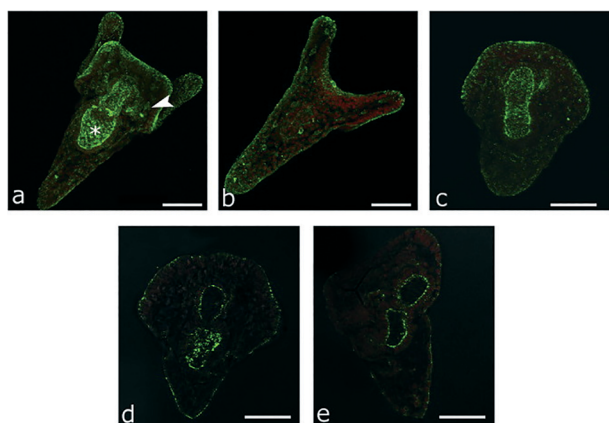

Fig. 4 Images from confocal laser scanning microscopy of choline acetyltransferase immunolocalization of larvae at the pluteus stage of P. lividus: a) control; b–e) anomalous larvae resulting from exposure to silica. Reproduced from ref. 62 with permission from Elsevier, copyright 2015.

EC_{50} results (Table 1) revealed that silica NPs were toxic for this organism. However, with increasing particle size (from nano to submicron size) and with surface functionalization (amine and hydrophobic moieties), the toxicity of the NPs decreased substantially, in particular with hydrophobic groups. The HASE-grafted NPs feature long alkyl chains, due to the macromonomer employed.

Canesi et al. evaluated the cytotoxicity effects of commercial Aerosil 200 silica NPs onto the Mytilus galloprovincialis mussel's hemocyte cells.[63] NPs were tested with concentrations up to 10 mg L^{-1}. Lysosomal membrane stability was not affected by the incubation with NPs. In contrast, lysosomal enzyme release and oxyradical production, both found to be NPs concentration dependent, nitrite accumulation (more prominent at the highest concentration) and a rapid increase of phosphorylation of p38 MAPK were induced by the silica NPs. Hence, silica nanoparticles did not induce significant cytotoxicity, but stimulated immune and inflammatory responses.

Effect on freshwater organisms

The toxicity of silica NPs towards freshwater organisms is summarized in Table 2. Wei et al. studied the effects of silica NPs (Sigma-Aldrich) and bulk particles (Shanghai Chemical Reagent Company of China) on the development of the green algae Scenedesmus obliquus.[64] Bulk particles had no effect on the algae growth, whereas silica NPs inhibited the growth by a maximum of 26%. Chlorophyll contents were decreased with increasing NPs concentration but not for the case of carotenoids. It is concluded that the NPs lead to some degree of toxicity in this case.

The ecotoxicity effects on Raphidocelis subcapitata, a microalga, was investigated by different authors. Hoecke found that smaller silica NPs were toxic towards this organism and concluded that the NPs adsorbed on the cell wall.[65] Book et al.[59] and Casado et al.[61] concluded that the EC_{20}/EC_{50} were high with many types of silica NPs, and thus they were not toxic towards the microalgae.

The silica effects on crustacean Daphnia magna were also extensively studied (Table 2). Bulk silica had no toxicity effects.[66] For silica NPs (Sigma-Aldrich), the EC_{50} for the

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Table 2 EC20 or EC50 of silica nanoparticles on different freshwater organisms

Organism	Silica type	EC$_{20}$ mg L^{-1}	EC$_{50}$ mg L^{-1}
Scenedesmus obliquus[64]	Commercial NPs 10–20 nm	144–48 h 217–96 h	—
Raphidocelis subcapitata[65]	LUDOX LS	20.0	—
	LUDOX TM40	28.8	—
	Bulk silica	>1000	—
	Sodium metasilicate pentahydrate	234	—
Raphidocelis subcapitata[61]	50 nm NPs	—	>100
	100 nm NPs	—	>100
Raphidocelis subcapitata[59]	Levasil CS30-236	295	—
	Levasil CS40-222	>500	—
	Levasil CS40213	>500	—
	Levasil CS50-34P	>500	—
	Levasil CS50-33P	>500	—
	Levasil CS25-436	>500	—
	Levasil CC301	>500	—
Daphnia magna[66]	Commercial NP	—	148.9
Daphnia magna[59]	Levasil CS30-236	—	>10 000
	Levasil CS40-222	—	>10 000
	Levasil CS40-213	—	>10 000
	Levasil CS50-34P	—	>10 000
	Levasil CS50-33P	—	>10 000
	Levasil CS25-436	—	>10 000
	Levasil CC301	—	>10 000
Daphnia magna[56]	NPs 14 nm	—	29.7
	Amine-modified NPs 22 nm	—	43
	Amine-modified NPs 292 nm	—	243
	Amine-modified NPs 448 nm	—	284
	HASE-grafted NPs	—	1140
Daphnia magna[61]	50 nm NPs	—	>1000
	100 nm NPs	—	>1000
Chlorella vulgaris[56]	Amine-modified NPs 292 nm	—	472
	Amine-modified NPs 448 nm	—	333
Oncorhynchus mykiss RTgill-W1 cells[59]	Levasil CS30-236	5.3	—
	Levasil CS40-222	6.0	—
	Levasil CS40-213	5.9	—
	Levasil CS50-34P	31.2	—
	Levasil CS50-33P	35.4	—
	Levasil CS25-436	5.2	—
	Levasil CC301	>100	—
Oncorhynchus mykiss RTG-2 cells[61]	50 nm NPs	—	>1000
	100 nm NPs	—	>1000
Thamnocephalus platyurus[61]	50 nm NPs	—	>1000
	100 nm NPs	—	>1000

smaller particles revealed that these were toxic at low concentrations only in the work of Clément et al.[56] In the remaining studies, silica NPs were found to be nontoxic for this organism. Lee and co-authors[67] measured an increased mortality rate of 5% with commercial fumed silica NPs and of 10% for commercial porous NPs (Sigma Corp.). Furthermore, growth and reproduction were not affected by silica NPs and there was no genotoxic effect.

Studies performed by Lee et al.[67] on *Chironomus riparius* larvae showed that neither fumed or porous NPs had genotoxic effects or induced changes in growth or reproduction. However, mortality increased by *ca.* 20% with the commercial porous NPs and *ca.* 5% with the fumed silica. The porous particles have almost 2-fold the surface area of fumed particles, however the authors were not able to correlate this property with the increased mortality.

The NPs tested by Clément et al.[56] with *Chlorella vulgaris* revealed that no EC result was obtained for the smaller, unmodified particles, whereas for larger amine-modified particles, fluorescence inhibition revealed an increased toxicity trend and the EC values tended to increase with size of the particles (Table 2).

Book et al.[59] tested different commercial NPs on *Oncorhynchus mykiss* RTgill-W1 cells, with the smaller NPs (17 and 18 nm) being extremely toxic towards these cells of the rainbow trout (Table 2). Casado et al.[61] found that amorphous silica NPs of at least 50 nm were not toxic towards *O. mykiss*'s RTG-2 cells, and EC$_{50}$ was higher than the highest tested concentration. Silica NPs were also not toxic towards the shrimp *Thamnocephalus platyurus*, with EC$_{50}$ values higher than the tested concentrations.[61]

Cytotoxicity and health effects of silica nanomaterials

Silica nanomaterials have raised some concerns regarding their safety to human health due to their increased production and presence in different goods and commercial products, as well as their potential application in therapy. The main routes of exposure for silica nanomaterials are inhalation, ingestion, skin penetration and blood circulation.[68] In the case of ingestion, SAS are well tolerated even at high contents and are included as additive in foodstuff and food packaging. However, their tendency to accumulate in the liver for long periods after repeated exposure has raised some concerns on the potential hepatotoxicity observed in some *in vitro* and *in vivo* studies.[69] Their possibility to cross the different biological barriers existing in every route of entrance, and to reach specific organs and tissues such as the lung alveoli or the intestinal epithelia, as for any other nanomaterial, will mainly depend on the size.[68,70] Moreover, independently of the route of entrance, some nanomaterials can reach the blood or the lymph and have a broad biodistribution.[71]

Some of the most relevant biological and health effects associated to silica NPs, apart from haemolysis, are neurotoxicity, lung cancer, fibrosis, renal injury or autoimmunity mediated by the activation of the NFκB pathway and the release of pro-inflammatory cytokines.[33,44,72] For instance, severe chronic lung inflammation has been associated to silica NPs inhalation, particularly to pyrogenic fumed silica, as well as an increased probability of developing autoimmune diseases after silica exposure during occupational settings.[33] However, as it was stated previously, not all the silica particles are toxic, and the differences found between them depend on their physicochemical properties (namely crystallinity, aggregation state and surface chemistry). In particular, the free silanol (non-hydrogen bonded) and siloxane groups, are the most relevant in terms of surface chemistry.[33,34] For silica, crystalline forms are significantly less soluble than amorphous forms, and thus the former are more toxic.[35,36]

Exposure to breathable crystalline quartz dust has been largely associated to silicosis, an ancient occupational disease. The silica dust is generated during the grinding, cutting or abrading of rocks containing quartz crystals and the exposure of workers to the breathable particles during those activities, or the manipulation of the silica powder, leads not only to silicosis, but also to other respiratory and systemic diseases.[33,44] Conversely, the exposition to breathable amorphous silica particles is largely accepted as safer because these particles can be cleared more rapidly from the lungs.[73] However, some studies have shown that crystallinity is not a clear factor associated with toxicity, but depends also on surface activity, the origin of the silica (processing pathway and environmental exposure) or the presence of some impurities, such as metal ions or mineral phases, among other factors.[74–76] The latter aspects are highly variable and are not intrinsically related with the silica toxicity itself but show that silica particles cannot be treated as a unique entity regarding hazard characterization.

Apart from crystallinity, the aggregation state is another relevant factor implicated in the toxicity of silica nanomaterials.[77] In fact, the reduced toxicity of SAS could be associated with the presence of secondary aggregates and agglomerates, that are formed from primary colloidal particles of nanometric size during the production process or under physiological conditions.[78] The exposure of different cell types to large aggregates showed a reduced toxicity and biological activity in comparison with their nanometric particle counterparts (≤100 nm) in suspension and small aggregates (>100 nm). However, except for very large aggregates (≥2 μm) that showed the lowest toxicity, there was not a correlation between the aggregate's size and the toxicological effects in the different cells tested.[78]

Recent studies suggested that the presence of free silanol but also siloxane groups and silica-derived radicals in the surface, seemed to be the leading cause of silica-associated toxicity. As a proof of concept, when silanol groups located at the quartz silica particles' surface were hindered by a coating, the toxicity of the material decreased.[79] In the case of CS, those functional groups are formed after fracturing of the crystals. In fact, quartz crystals of breathable size and intact surface generated by a synthetic procedure, did not cause toxicity to macrophages or haemolyses *in vitro*, contrary to the effects observed with quartz dust or the same synthetic crystals after being fractured.[80] Crystal fracturing induces some structural defects, a higher heterogeneity of the silanol acidic sites and silicon oxygen radicals in the surface (surface bound reactive oxygen species, ROS).

These surface groups also increase the interaction of amorphous silica NPs with the cell membranes and the associated membranolytic effect that causes haemolysis and cytotoxicity (Fig. 5). In SAS particles, free silanol and siloxane groups are frequent due to the lack of order, and the density of those groups largely depends on the synthetic route.[81,82] Free silanols are usually present in higher contents for silica NPs processed at lower temperatures like precipitated and colloidal silica. Three different silanol groups are
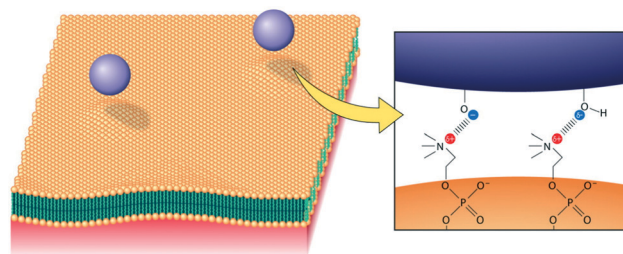

Fig. 5 Schematic representation of the interaction mechanism of silica NPs and cellular membranes at physiological pH: membrane phospholipids interacts either with deprotonated geminal and vicinal silanols through ionic interactions, or with isolated silanols through hydrogen bonds. Reproduced from ref. 87 with permission from Elsevier, copyright 2016.

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distinguished (isolated, germinal and vicinal) with varying hydrogen bonding, charge and hydrophobic patterns that influence the SAS-cell interactions.[34,76] Hydroxyl radicals generated by SAS are promoted by the presence of siloxane networks formed by interconnected rings of 2 or 3 members instead of 4 or more members. Highly strained rings of 2–3 members are more often present in SAS obtained at high temperatures like fumed silica. After cleavage of these highly strained rings, silicon-oxygen radicals are formed in the surface of silica particles that react with water molecules to form hydroxyl radicals. Likewise, reactive oxygen species (hydroxyl radical, superoxide anion, hydrogen peroxide, and singlet oxygen radicals) are also induced in cells exposed to the silica nanomaterials. Hence, ROS release is one of the leading mechanisms related with silica cytotoxicity and haemolysis, among other cellular effects.[33,34,44] Yet, toxicological effects without ROS induction have also been described such as cytotoxicity or genotoxicity induced by SAS of ≤40 nm.[44]

The use of metal doping or surface modification with polymers or organic molecules that interact with the free silanol and siloxane groups are among the proposed strategies to reduce the toxicity of all types of silica nanomaterials.[47,82,83]

MS NPs have also some free silanol groups on the surface that depend on the synthetic route, as in the case of SAS. However, the average density and the accessibility of those groups to the cells are lower than in the non-porous silica nanomaterials, significantly reducing the haemolysis of mammalian red blood cells.[77,84] The reduction in MS NPs size results in an increased haemolytic activity.[85] Besides, they have also a homogeneous and tuneable pore structure, high drug-loading capacity and they are easy to produce with a good control of the morphology. For those reasons, MS NPs are one of the most explored nanomaterials for biomedical applications.[47] However, the low biodegradability of these NPs is a drawback on their translation into clinical applications because their bioaccumulation causes toxicity to the organs affected, mainly liver and spleen. Thus, strategies to increase their biodegradability are being explored.[86]

Cytocompatibility of silica aerogels

Regarding silica aerogels, as already mentioned, they should be considered in general as an engineered material composed by SAS NPs from a toxicity evaluation point of view. Moreover, the dusty feature of silica aerogel particles can particularly produce a dry sensation in the skin and irritation by friction.[88–97]

Table 3 Cytocompatibility tests with different cell types in the presence of silica aerogels and silica-containing hybrid aerogels

Aerogel type (concentration in cell test)	Method of synthesis/characterization[a]	Cell type	Cell viability (incubation time)
Silica[97] (1–1000 µg mL^{-1})	n/a	Breast cancer cells (MCF7)	90–100% (72 h)
Silica[96] (0.25–4.0 wt%)	Sol–gel and APD using rice husk ash as silica source/D: 0.08 g cm^{-3}, 7.64% silica, PS: ~80 nm	Dermal fibroblast cells (HSF 1184)	100–120% (24 and 48 h)
Silica[98]	Sol–gel and freeze-drying/SA: 100.53 m^2 g^{-1}, PS: 3.74 nm	Embryo fibroblast cell line (3T3-L1)	70–80% (24, 48 and 72 h)
Silica[92] (5–20 mg mL^{-1})	Sol–gel and spray-drying/mesoporous, SA: 500–1200 m^2 g^{-1}, porosity 80–99.8%, D: 0.003 g cm^{-3}	Colorectal adenocarcinoma (Caco-2)	75–105% (24 h)
Dextran-coated silica[92] (5–20 mg mL^{-1})		Colorectal adenocarcinoma (Caco-2)	65–110% (24 h)
APTES-modified silica[92] (5–20 mg mL^{-1})		Colorectal adenocarcinoma (Caco-2)	65–130% (24 h)
Silica loaded with resveratrol[91] (2.5–20 µg mL^{-1})	Sol–gel and freeze-drying	Chondrocyte cell line (TC28a2)	90–100% (24, 48 and 72 h)
Silica with and without hydroxyapatite in HA/SiO$_2$ weight ratios: 0–1.3 (ref. 94 and 95)	Sol–gel and APD/D: 0.0915–0.1127 g cm^{-3}, depending on HA/SiO$_2$ ratio	Dermal fibroblast cells (HSF 1184)	100–180% (24 and 48 h)
		Osteoblast cells	100–140% (24 and 48 h)
Polyurea-nano encapsulated silica[102]	Sol–gel and APD/macroporous, D: 0.66 g cm^{-3}, P: 50.0%, PS: 5 µm	Bone marrow microvascular endothelial cell line (BMEC)	92–96% (72 and 120 h)
		Umbilical vein endothelial cell line (HUVEC)	96–97% (72 and 120 h)
Silica-gelatine[93] (0.5–2.0 mg mL^{-1})	Sol–gel and co-gelation/mesoporous, SA: 300–500 m^2 g^{-1}	Squamous cell carcinoma (SSC VII) and promyeloblast cell line (HL-60)	80–100% (24, 48 and 72 h)
		Keratinocyte cell line (HaCaT)	80–100% (24, 48 and 72 h)
Chitosan–silica[99]	Sol–gel and supercritical drying/SA: 470 to 750 m^2 g^{-1}	Mammal cells	Score:1 out of 4 – very slight cell damage Highly haemolytic

[a] APD: ambient pressure drying, D: density, P: porosity, PS: pore size, SA: surface area, n/a – not available.

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Silica aerogels and hybrid aerogels containing silica have been tested regarding cytocompatibility with several cell lines (adipose tissue, fibroblasts, blood, neurons, osteoblasts, keratinocytes, endothelial cells, chondrocytes, tumour cells).[91,93,95,97–103] In general, silica-based aerogels presented good cytocompatibility with cell viabilities above 90% (Table 3) and have been even proposed as scaffolds to promote cell growth and proliferation for the ultimate goal of tissue growth or as artificial heart valve leaflets.[94–96,98,102,104] Silica aerogels have been also proposed as a non-cytotoxic and safe carrier or vector of different drugs (resveratrol, 5-fluorouracil, paclitaxel, methotrexate) for local and systemic administrations.[91–93,97] Interestingly, the biological response of some hybrid aerogels can differ from the behaviour of their individual counterparts.[99] The incorporation of increasing contents of hydroxyapatite (HA) in silica aerogel networks at weight ratios up to 1.3 also resulted in higher viabilities and growth of fibroblasts and osteoblasts than those of silica aerogel and hydroxyapatite individually, following increasing trends up to 0.5 where a maximum was reached.[94,95] Moreover, the incorporation of silica aerogel particles into certain polymeric materials (poly(ε-caprolactone)) may interfere in the cell regulation mechanisms.[101] Silica aerogel may neutralize acidic degradation products of polymers in the cell microenvironment with a beneficial effect on the cytocompatibility of the resulting material, although at the expense of a delayed cell growth at least at the early culture stages. Finally, polyurea-reinforced silica aerogels had blood and cellular compatibility and did not inhibit the normal function of platelets and vascular endothelial cells.[102]

Workplace safety regulations

Since the first day of 2020, nanomaterials fall within the scope of REACH and classification, labelling and packaging (CLP) regulations, and manufacturers/importers of nanoforms in the EU have to comply with reporting obligations such as the registration of the nanomaterials, chemical safety assessment and the characterization of the nanoforms.[105]

Due to the concerns posed to human health, working with silica must follow several restrictions. When working with nanoparticles and their agglomerates, our knowledge of the effects of these materials on health becomes scarcer and greater precautions should be taken. Even in its less toxic amorphous forms, like in silica-based aerogels and many silica NPs, cumulative exposure of inhalable silica poses a threat to worker's health. Although there are several forms of exposure, as referred in the previous section, silica inhalation is the most important one. Free silica in the air should be measured in workspaces where its presence may be relevant, in order to ensure that there are no exposure problems. Table 4 summarizes some standards on the workplace exposure limits for amorphous silica airborne particles, which are the most significant regarding silica aerogels production and storage. Other types of silica particles are also included for comparison.

Health surveillance measurements to safeguard workers from the risks they incur at the workplace is mandatory by law.[106] To comply with the exposure limit values from Table 4, and to ensure the safety of workers, it is necessary to assess, monitor and minimize the risk of exposure. Standards such as ISO/TR 12885, ISO/TS 21623, EN 13263, CEN/TR 13205 and CEN/TR 15278 from the International Organization for Standardization (ISO) and the European Committee for Standardization (CEN) provide guidelines on how to monitor the exposure and assess the risks of nanomaterials and silica particles in the workplace. Recently, the ISO/TS 21361:2019 standard was issued, which defines a method to identify and quantify air concentrations of amorphous silica nanoparticles by size in a mixed dust industrial manufacturing environment, by using an electrical low-pressure cascade impactor for sampling the particles, followed by TEM and EDS analyses.

In addition, CEN has published CEN/TR 15419 and EN 1073 standards on the requirements and selection of protective clothing for workers in order to minimize the risk of exposure.

Two studies are here described to illustrate the effective exposure to SAS NPs and silica aerogels in the workplace.

Table 4 Standards on the workplace exposure limits for amorphous silica airborne particles, as an eight hour timed weighted average (8 h TWA). Crystalline forms were included for comparison

Standard	Silica type	8 h TWA
OSHA Standard 1910 subpart Z – toxic and hazardous substances[107]	Amorphous, including natural diatomaceous earth	20 mppcf[a]
		8 mg m^{-3}
	Quartz (respirable)	10 mg m^{-3}
HSE Standard EH40/2005 – workplace exposure limit[108]	Silica, amorphous inhalable dust	6 mg m^{-3}
	Silica, amorphous respirable dust	2.4 mg m^{-3}
	Crystalline respirable	0.1 mg m^{-3}
	Fused, respirable dust	0.08 mg m^{-3}
	TEOS-based	5 ppm
		44 mg m^{-3}
Directive (EU) 2017/2398	Crystalline respirable	0.1 mg m^{-3}
Limit values for occupational exposure[109]		
Occupational Exposure Limits in EU 27 (ref. 110)	Silica, amorphous respirable	0.3–4 mg m^{-3}
	Fused silica, respirable	0.08–4 mg m^{-3}

[a] Millions of particles per cubic foot of air, based on impinger samples counted by light-field techniques.

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Oh et al.[111] compared the exposure to silica NPs in two plants, each using a different synthesis procedure: a fumed silica plant (pyrolysis) and a sol–gel based plant (polymerization process). It was found that the exposure to the NPs occurred in the packaging process and so these were quantified. The concentration of airborne silica NPs was found to be 0.4 mg m^{-3} in the fumed silica plant and 11.3 mg m^{-3} in the sol–gel plant. Furthermore, the average diameter (of airborne particles) of the sol–gel manufactured particles was greater than that of the fumed silica ones (94 vs. 64 nm). However, the former silica agglomerated into clusters up to a few microns in diameter, while the fumed silica agglomerates are only a few hundred nanometres in diameter. These results indicate that, in the sol–gel silica nanoparticles plant, the workers are exposed to concentrations higher than some of the limits for amorphous silica in Table 4, increasing the risks of health effects. However, due to the formation of agglomerates, the particles might not be inhalable. In another study, a health evaluation report from NIOSH reveals that airborne amorphous silica concentration at a training facility of silica-based aerogel insulation materials approached occupational limits and that the particles released by the aerogels were respirable.[112] In fact, most workers manifested symptoms associated to the exposure to this type of SAS NPs, such as very dry skin and upper respiratory track irritation.

Regarding silica aerogels, there is a lack of legislation and standards. The only standard that refers to this type of material is focused on the determination of physical properties of aerogel blankets for buildings thermal insulation (ISO/DIS 22482), but it is still under development. In fact, thermal insulation of buildings is a prime application of silica aerogels, and in the particular case of construction products, workers' exposure to powdered silica is of major concern, as the probability of releasing particles from the materials significantly increases due to cutting/polishing operations. The regulations already mentioned in this section for amorphous silica NPs also apply to this situation if the activities are performed in closed compartments, but when activities are performed outdoor it is more difficult to define concentrations.

When applied in construction, aerogels must be also characterized relatively to the release of dangerous substances, based on requirements for Construction Product Regulations.[113] Characterization of the release of dangerous substances to the indoor environment is a relevant issue for construction materials. There is no European harmonized test method available yet for this type of assessment. Therefore, testing methods according to ISO 16000 (ref. 114–116) are used today. At the moment, maximum permitted levels of release of dangerous substances are provided in national regulations. Based on the Technical Report 034† of the European

Organization for Technical Assessment (EOTA),[117] aerogel-based products for indoor use must be tested with respect to the emission of volatile organic compounds (VOC). EOTA TR034 gives a general specification guidance to decide which assessment methods should be taken into account for dangerous substances in products/product families.[117] Hereby, aerogel-based materials belong to products with indirect contact to indoor air. They are covered with other products but nevertheless could release dangerous substances to indoor air. Classification criteria for emission of volatile organic compounds (VOC) is specified according to EOTA TR 034 (ref. 117) for Belgium, France, Germany and Poland. These countries consider different evaluation procedures as well as partly different substances.

Safety practices when handling silica aerogels

Usually, the exposure to silica nanomaterials in workplace occurs during the handling stages of the manufacturing process as, in many cases, the synthesis stages occurs in closed vessels. Ventilation, keeping workspaces and workwear tidy and using personal protection equipment (PPE) are effective ways to minimize the exposure.[118] The exposure to NPs can also be controlled with project design: plant layout, ventilation and air purification systems, technology selection and modifications have a major impact on the quality of the air in a workplace. Confinement of the harmful nanomaterials in specific facilities is also important. This can be achieved by having the manufacture process disconnected from common areas (like cafeterias) and administrative buildings, and promoting hygiene practices like decontamination and wearing specific garments for the nanoparticle-laden areas.[118,119]

Most of aerogel-based products can develop dust release during production, transport, cutting or handling. Hereby, it would be reasonable to measure concentration of particles with different sizes for investigated scenarios. It is meaningful to consider coarse, inhalable particles with a diameter between 2.5 and 10 μm (fraction PM10). Furthermore, fine particles with diameter smaller than 2.5 μm have great importance to be analysed because of their capability to penetrate to alveoli. Ultrafine particles with diameter smaller than 0.1 μm have crucial relevance for measurement because they can reach the cardiovascular system. Moreover, it is reasonable to analyse chemical composition of produced dust by means of an EDX-spectrum. This evaluation is very important, since high concentration of airborne silica and respirable particles were found in plants working with silica nanostructures, as documented in the previous section.

When handling aerogel-based materials, PPE per manufacturer's safety data sheet must be wore[112] to avoid respiratory irritation and very dry skin. Employers should make a risk assessment and ensure that exposure is prevented or controlled. Training of the employees and a

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† Technical Report 034 is superseded by EOTA Guidance Document GD 014 in 2019. GD 014 is a general guidance on how to deal dangerous substances in European assessment documents (EAD) and European technical assessments (ETA). Assessment methods concerning the release of dangerous substances for aerogel-based materials in their first EADs/ETAs will be based on EOTA TR 034.

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regular evaluation of the implemented practices are of upmost importance.[112,120] Aerogel-based materials must be stored in closed packagings. It is recommended to unpack material in the work area shortly before handling. Workers must wear CE-approved respirators, safety glasses or chemical goggle, disposable coveralls, impermeable inner gloves, cut-resistant outer gloves and impermeable shoes. Aerogel-based material should be die-cut if it is technically possible. Local exhaust ventilation in the workplace is the most effective way to minimize exposure to dust. Moreover, dry vacuuming with a commercial HEPA-filter is the better way for dust cleaning when compared to sweeping or cleaning with water.[120] After the handling of aerogel-based materials, operators must thoroughly wash face and hands as well as all dusty areas of skin or clothing. When the released silica is hydrophobic, washing hands with water and soap is not always very effective and the excessive hand washing and mechanical friction was shown to cause dry skin.[112] Other more effective cleansers should be considered for this case, which should also minimize hands dryness.

Guidelines for disposal of silica aerogels

As it was highlighted in the Introduction section, silica-based aerogels are amazing materials for a wide range of applications. However, this brings out a non-neglectable issue related with the disposal of these solid matrices. Although these polymers are not biopolymers, they suffer spontaneous degradation in water and soil.[121] It is known since the second half of the last century[35,122] that silica is soluble in water, suffering degradation *via* hydrolysis of siloxane bonds, forming monosilic (or polysilic) acids.

$$(SiO_2)_x + 2H_2O \rightleftharpoons (SiO_2)_{x-1} + Si(OH)_4 \qquad (1)$$
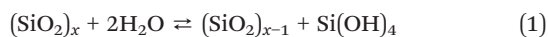
Monosilicic acid (also called orthosilicic acid) is a weak acid (pK_a = 9.8) with silicon tetrahedrally coordinated to four hydroxyl groups.[35] The silicic acid is non-toxic[37,38] and can be used as a source of soluble silica,[76] making the hydrolysis process a natural route for degradation of silica either in water or in soils. However, $Si(OH)_4$ in only stable in water, at room temperature, at concentrations below 1 mg L^{-1}. At higher concentrations, the orthosilicic acid undergo polymerization.[123]

The effect of molecular weight on the environmental behaviour of the most common organosilicon polymer – the poly(dimethyl siloxane) (PDMS) – has been evaluated by Graiver *et al.*[121] Independently of the molecular weight (up to

400), organosilanes suffer hydrolysis, characterized by an activation energy ranging from 14–24 kcal mol^{-1} (ref. 124 and 125), followed by condensation (Scheme 1); additionally, a phase separation occurs due to their limited solubility in water (<1.0 ppb) and low density (<1 g cm^{-3}).[121] This leads to a very low environmental impact in aquatic ecosystems.[126] However, in the soil, the environmental impact is somewhat different. Lower molecular weight PDMS materials in soil can undergo two different processes: hydrolysis and evaporation.[127] Since the evaporation rate is higher than the hydrolysis rate,[128] low molecular weight PDMS tends to evaporate to atmosphere, being oxidized by hydroxyl radicals (the life time of PDMSs in atmosphere is no longer than 10–30 days).[129,130] On the other hand, high molecular weight organosilicons are not volatile and, consequently, remain in water or soil, where they eventually suffer hydrolysis.[131,132]

Recently, Rücker and Kümmerer published a thorough review entitled "Environmental chemistry of organosiloxanes".[133] In this article aspects related with the toxicity, accumulation, and degradation of organosiloxanes (either oligo or polysiloxanes), *i.e.*, silica-based species also containing Si–O–C bridges, were covered. Thus, the persistency, bioaccumulation and Si–O cleavage reactions (*e.g.*, by enzymes,[134] thermal degradation[135] and by using fluoride[136]) have been reviewed.

It is worth noticing that despite the non-toxicity of these materials, they are not eliminated and, consequently, remain in the environment where the overall ratio between essential elements and silicon may change and does affect the human well-being.[132] Thus, the research on the degradation and/or reuse/recycling of silica-based materials, including aerogels is, in our opinion, challenging and a hot topic for the next few years, as a consequence of aerogels application widening to different fields. In this section we focus on recent developments on the disposal of silica-based materials.

The disposal of silica aerogels has not been yet focused in the literature, although different approaches for the disposal or reuse of silica-based materials through physical, thermal or chemical treatments can be extended to aerogels. This issue is of outmost importance due to the impact that silica-based materials might potentially have on human health and environment, as already shown in this review. Even so, many questions related with the biosafety of silica NPs remain veiled.[137] Thus, the accumulation of end-life silica-based aerogels is an urgent issue that must be faced by the society. As with other wastes, two different approaches can be made: the treatment and disposal or the reuse.

Concerning the disposal, the deposit in landfills is a common strategy to deal with these compounds.
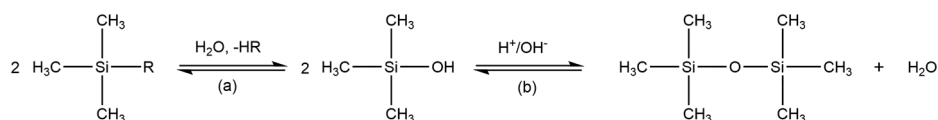

Scheme 1 Representative (a) hydrolysis and (b) condensation reactions of monofunctional silanes.

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Furthermore, the presence of siloxanes into landfills reflects the increasing consumption of silica-based products, either by the industry and buildings or consumer purposes.[138] However, some problems arise from that approach, especially because low molecular weight silica volatile compounds are formed during the anaerobic stage occurring in landfills.[139] For example, McBean *et al.* have demonstrated that the presence of siloxane-based materials in the solid waste landfills leads to significant concentrations of volatile methylsiloxanes in biogas, causing relevant operational damages particularly due to the formation of silica deposits in pipelines with a consequent impact in engine and turbine performances.[140,141] Another alternative is the thermal recycling/degradation of silica-based materials. The thermal degradation of, *e.g.*, poly(methylphenyl silane), shows that the Si–Si cleavage occurs at temperature around 400 °C, with an onset degradation temperature of approximately 300 °C.[142] However, this process is not effective, corresponding only to a small fraction of the weight loss percentage of the polysilane. Furthermore, thermal decomposition, which may also include incineration, leads to an increase in the carbon dioxide emissions.[133] Another alternative for aerogels

disposal is the waste-to-energy (WtE) combustion.[143,144] Although WtE conversion is, in general, related to the incineration of municipal wastes, it can be used in other industries, including cement and steel ones, allowing an increase in the heat recovery and energy saving. This strategy applied to heavy industries, processing in continuous, aims at medium and long term, to reach zero emissions and wastes.

The depolymerization methodology has been used to overcome the abovementioned drawbacks. This approach allows the recycling of end-of-life products for the production of new polymers. Several depolymerization pathways and reagents have been tested.[145–147] Döhlert *et al.*[148] have shown that boron trifluoride dietherate ($BF_3 \cdot OEt_2$) is able to break the siloxane bond in hexamethyl disiloxane (**1**) – Scheme 2(a). Based on this, the depolymerization of poly(dimethyl siloxane) (**4**) has also been successfully tested (Scheme 2(b)). The reaction yields are dependent on the mass balance of reagents and reaction time; however, for the optimized conditions (shown in Scheme 2), yields of >99% and 86% were obtained for the fluorotrimethyl silane (**3**) and difluorodimethyl silane (**5**), respectively.
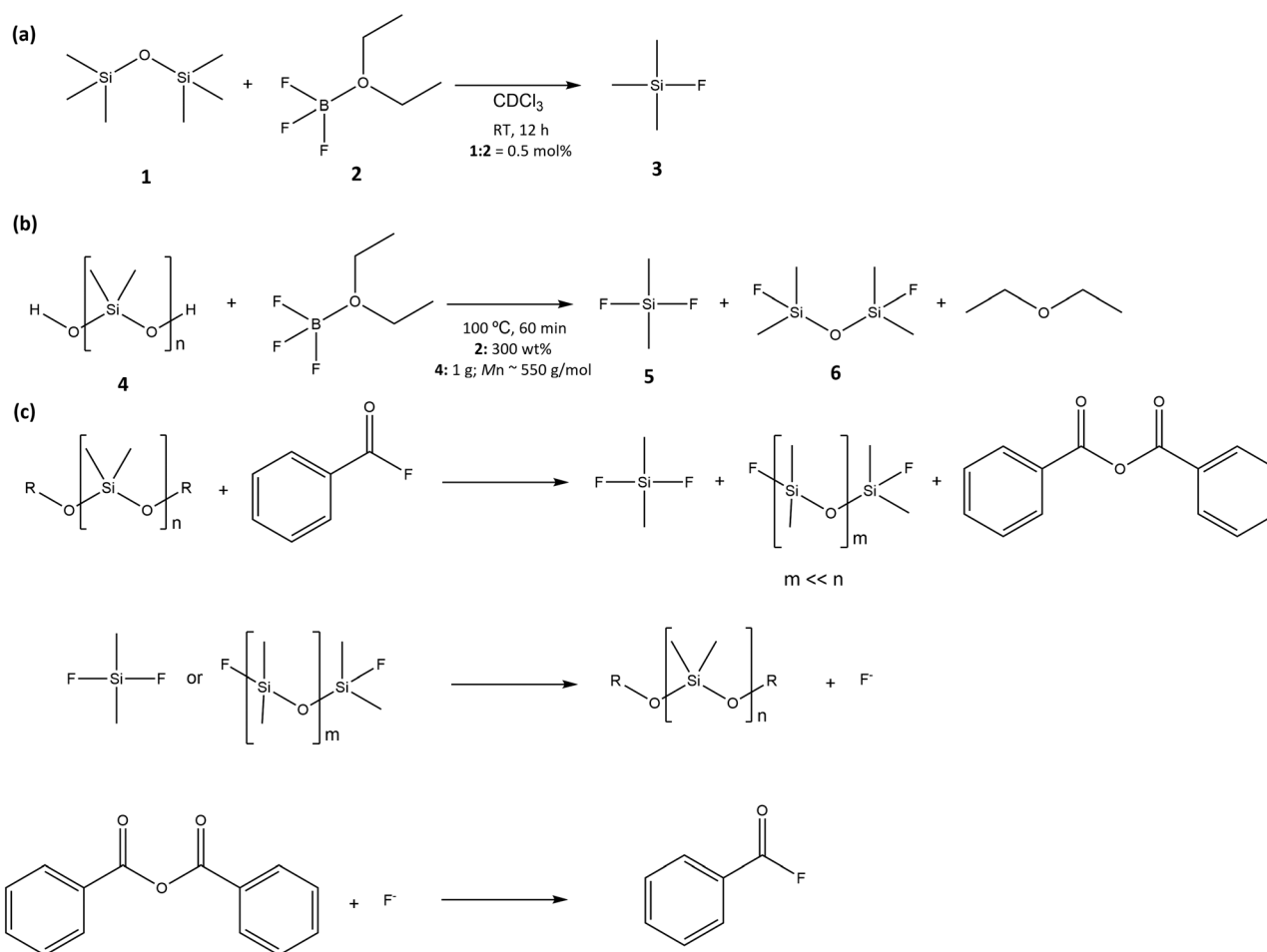
Scheme 2 (a) Reaction of hexamethyldisiloxane (**1**) with boron trifluoride diethyl etherate (**2**); (b) depolymerization of polysiloxane (**4**) with boron trifluoride diethyl etherate (**2**); (c) depolymerization circular approach for the conversion of polysiloxanes. Reactions (not balanced) proposed by ref. 148.

Following this work, the same group has concluded that the depolymerizing effect of $BF_3 \cdot OEt_2$ (2) does not depend on the structure of the polysiloxane, thus it can also be used for branched and crosslinked polysiloxanes.[147] In all reported cases, the depolymerization products can be used for the synthesis of new high-quality polymers.

Another important issue related with the treatment or depolymerization of silica-based polymers is the high temperature needed. This leads to a high energy consumption and, consequently, to high process cost. Therefore, to perform the depolymerization at low temperatures (say lower than 150 °C) is a challenge. A methodology to achieve that has been devised by Enthaler and co-workers by using metal-based catalysts.[149–151] Based on previous works on depolymerization of, e.g., polyethers,[152,153] by using zinc and iron salts as catalysts, a comprehensive and systematic study was carried out by testing the performance of those catalysts and different reagents on the depolymerization of polysiloxanes. In this respect, different polysiloxanes have been depolymerized by using zinc trifluoromethanesulfonate as catalyst and benzoyl fluoride as depolymerization agent, showing that, in general, the reaction yields are very high (>80%), independently of the molecular weight and pending groups of the polysiloxane.[150] This work was further extended to check the effect of iron salts (as, for example, $FeCl_3$, iron(II) acetate and iron(II) acetylacetonate) and different depolymerization reagents (e.g., benzoyl fluoride, and acid chloride/potassium fluoride).[151,154] Following a similar methodology, the effect of iron salts, such as iron(III) and iron(II) chloride, iron(III) fluoride, iron(III) oxide and iron(II) acetate, was tested. Concomitantly, the influence of the substitution of the phenyl ring of benzoyl chloride by other functional groups (e.g., dimethylphenyl) was also studied. Benzoylchloride and FeF_3 provided the best conditions in terms of depolymerization yield for the formation of dichlorodimethylsilane.[147] This strategy, based on the cleavage of a Si–O bond to produce a Si–X bond (X:F or Cl)[155,156] allows to aim the reuse of monomers to produce new polymers[155] as well as to obtain conditions for the production of benzoyl chloride or fluoride (see Scheme 2(c)), and thus to achieve a circular approach.

A different strategy for cleavage of Si–O–Si bonds was demonstrated by Zuo et al.[157] By using a green and strong oxidant – the oxone – the cleavage of the siloxane bridges existing in a poly(siloxane-thioether) was observed, suggesting that such route can be used for the breakup of the polymer to produce monomers.

Despite the different possible routes and strategies for the disposal or reuse of silica-based aerogels, a holistic approach for a cradle-to-grave cycle is demanded from a practical point of view. Motivated by the excellent performance of aerogel monoliths for the remediation of oil spills, when compared with polyurethane or polypropylene, a life cycle assessment (LCA) of aerogels has been performed in detail.[144] Although we do not go deep on that topic here, that study assumes that aerogels are synthesized by mainly using TEOS and TMOS as precursors and different fabrication approaches, including the carbon dioxide supercritical and alcohol supercritical extractions. Following this assumption, they have concluded that the disposal of aerogels leads to a benefit in terms of net energy, greenhouse gas emissions and less solid wastes generation, when compared with polyurethane foams. There are several other ways to decrease the pollution footprint. For example, Huber and co-workers showed that a modification of the silica aerogel synthesis following a one-pot route together with the solvent and silylation agent recycling (ethanol and hexamethyldisiloxane), in ca. 98%, allows a decrease in the CO_2 emission in 28%, from 8.8 to 6.3 kg per kg of aerogel, taking as reference the so-called "classical case".[158]

The latter two examples show that there is still some way to go towards the optimization of the ecological footprint related with the synthesis and application of silica-based aerogels, which worths the attention of the researchers, given the relevant and unique properties of these materials.

Final remarks

This review article aimed to gather all the available information in the literature regarding toxicity (ecotoxicity and cytotoxicity), workplace safety regulations and safe handling practices of silica-based aerogels, as well as their disposal alternatives. It was a needed and urgent work, considering the lack of guidelines for toxicity and safety issues on these nanostructured materials and their raising applications. Since the very beginning the authors perceived that the referred information was inexistent or scarce for certain aspects. Thus, considering that the main problem of aerogels in this regard is their particle shedding, the authors considered the already existing knowledge on toxicity and safety regulations for synthetic amorphous silica nanoparticles. Indeed, silica aerogel structure is composed by ramified chains of amorphous silica nanoparticles of some tens of nanometres in diameter. The connecting necks of the pearl necklace-like chains of silica aerogel structures are very fragile, thus small clusters of these nanoparticles detach from the network and easily spread in the air due to their very low size/weight.

Although the amorphous silica is recognized by the scientific community as much less problematic than crystalline silica in terms of safety, the information given in this overview shows that there are studies confirming some degree of toxicity of the former, either to environment ecosystems or some human cells. Moreover, it was documented with one example that silica-based aerogels can release a high number of particles when handled. Thus, it is of primary importance to wear personal protective equipment and to monitor and ventilate the workplaces where these materials are handled/stored, in order to prevent reaching the exposure safety limits for amorphous nanoparticles. These nanoparticles may cause

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symptoms like very dry skin and upper respiratory track irritation. Still, it is worth noting that these effects may change according to the size and surface chemistry of the released particles.

Regarding the disposal of silica aerogels, although the deposit in landfills is a common strategy for the end-of-life of silica aerogels, problems arise from that approach, since low molecular weight silica volatile compounds are formed during the anaerobic process. The most interesting approach for end-of-life of aerogels is the depolymerization of the siloxane bonds in order to provide recycled monomers/oligomers for new aerogels production, allowing a circular economy rationale.

Finally, this work has shown that there are many steps yet to be taken in the domain of safety and toxicity of aerogel materials to fill the gap of information in this regard. Studies with new and already known aerogel materials are very relevant, in order to set the limits for their use and take full benefit of their amazing properties and performance in many application areas.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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