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Mini-review

Transport routes of metalloids into and out of the cell: A review of the current knowledge

Ronen Zangi [a,b,*], Montserrat Filella [c,d]

[a] Department of Organic Chemistry I, University of the Basque Country UPV/EHU, Avenida de Tolosa 72, 20018 San Sebastian, Spain
[b] IKERBASQUE, Basque Foundation for Science, 48011 Bilbao, Spain
[c] Institute F.-A. Forel, University of Geneva, Route de Suisse 10, CH-1290 Versoix, Switzerland
[d] SCHEMA, Rue Principale 92, L-6990 Rameldange, Luxembourg

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ABSTRACT

Except for their extra- and intra-cellular interfaces, cell membranes are hydrophobic and inhibit the transport of hydrophilic molecules. Metalloids in aqueous solutions form chemical species with oxygen and hydroxyl groups and, therefore, exist as hydrophilic neutral polar solutes or as hydrophilic anions. This characteristic of metalloids introduces a large barrier for their passage through the cell membrane via unaided diffusion. The necessity for an uptake mechanism for metalloids arises from the requirement of these species for the maintenance of life, such as the need of boron for plant cells. Conversely, the transport of these species out of the cell is necessary because some metalloids are toxic, such as arsenic and antimony, and their entrance into the cell is undesirable. The undesired uptake of these toxic species is possible via pathways designed for the uptake of other structurally and chemically similar essential compounds. Therefore, the extrusion of arsenic and antimony out of the cell is an example of a detoxification mechanism. As a consequence of the hydrophobic character of the cell membrane in all living systems, the main route for the uptake and efflux of metalloids is facilitated by transmembrane proteins, driven either by concentration gradients or by energy-fueled pumps. However, metalloids forming or embedded in nano-sized particles escape the need to cross the cell membrane because these particles can be taken into the cell by endocytosis. Here, we review the uptake and efflux pathways of boron, silicon, arsenic, and antimony through the cell membranes of different organisms and the protein channels involved in these processes. In particular, passive diffusion via aquaglyceroporins, active transport via primary and secondary ion pumps, extrusion into vacuoles of metalloid-thiol conjugates via ATP-binding cassette, the efflux of methylated metalloids, and endocytosis are summarized.

Contents

* Corresponding author at: Department of Organic Chemistry I, University of the Basque Country UPV/EHU, Avenida de Tolosa 72, 20018 San Sebastian, Spain. Tel.: +34 943018112.
E-mail address: r.zangi@ikerbasque.org (R. Zangi).

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Metalloids are elements that are neither metals nor nonmetals. This group is composed of boron, silicon, germanium, arsenic, antimony, and tellurium, which form a diagonal line in the periodic table of the elements. The biochemical processes of different organisms have evolved to take advantage of some of these metalloids, but other metalloids can interfere with and disrupt these processes. For example, boron and silicon are essential, or at least beneficial, for plants, whereas arsenic and antimony are toxic. The abundance of these metalloids in the environments of living organisms is changing due to both geochemical and anthropogenic processes. Consequently, an increase in the availability of metalloids that can harm essential cellular processes can account for life-threatening situations, such as in the case of arsenic. The simplest adaptation in the organism would be to control the transport of these metalloids into (uptake or influx) and out of (efflux) the cell. Because different metalloids have different known impacts on living systems and on humans in particular, the extent of the research aimed at elucidating the biological aspects of these metalloids varies significantly. Moreover, the recent exponential growth of nanotechnology applications has added a new field investigating the participation of engineered nanoparticles in biological processes. In this review, we summarize the current knowledge about the influx and efflux mechanisms of boron, silicon, arsenic, and antimony.

1. Biological activity of metalloids

The four metalloids that are the focus of this review have very different distributions and biological activities. Boron is widely distributed (5–100 mg/kg) in the earth's crust. At a neutral pH, it exists primarily as boric acid, $B(OH)_3$, and in a much smaller amount as the conjugated base, the borate anion $B(OH)_4^-$ ($pK_a = 9.2$). For all plants, boron is an essential element, but the requirement for boron varies greatly from plant to plant. Boron is involved in the structure and function of the cell walls, membrane function, and metabolic activities, and it is critical for high yields of quality crops [1,2]. Boron deficiencies result in many anatomical, biochemical and physiological changes in plants. However, the biochemical action of boron is not clear. Boron's essentiality is thought to derive from its ability to form diester bridges between *cis*-hydroxyl-containing molecules and, thereby, act as a 'molecular linker' [3]. This ability, for example, is required in the cross-linking of the polysaccharide rhamnogalacturonan, which is a crucial component of the plant cell wall. In addition, there is evidence that boron is nutritionally important for animals and humans; however, it was considered only 'probably essential' until now. Boron has been observed to affect mammalian life processes via metabolism or the utilization of numerous substances, including other minerals such as calcium and magnesium, as well as, sugar and hormone molecules [4,5]. Boron's mode of action is not known; however, it is hypothesized to play a role in the function of the plasma membrane [2,5].

Silicon is the second most abundant element, after oxygen, in the earth's crust. In aqueous solution, silicon exists in the form of silicic acid, $Si(OH)_4$. Except in lower plants, such as diatoms, silicon is not considered an essential element due, in part, to insufficient data on its metabolism. However, silicon is found in higher plants and animals and is considered beneficial for both. In plants, the extent of silicon accumulation differs among different species. Rice, one of the highest silicon-accumulating plants, can have a silicon content that is higher than the levels of essential nutrients, such as phosphate, nitrogen, and potassium [6]. Silicon is known to enhance the resistance of plants to pests, diseases, and other stresses [7,8]. For example, a mutant rice plant, *Oryza sativa*, which is missing the silicon transporter Lsi1 and is, therefore, defective in $Si(OH)_4$ uptake, suffers from reduced grain yield and an increased susceptibility to pests and diseases [9]. At high concentrations $Si(OH)_4$ can polymerize to form poly-silicic acid, a structural component that functions in the defense against biotic and abiotic stresses [10]. Silicon is also beneficial for animals. For example, in humans, silicic acid is important for the development of bones and is present in nearly all connective tissues, suggesting an important function in structure, stability and elasticity. More specifically, the oral intake of silicone was reported to have a significant positive effect on the skin surface and skin mechanical properties and on the brittleness of hair and nails [11,12].

Arsenic is widely distributed in the earth's crust and exists in four oxidation states: +5, +3, 0, and −3. However, the most abundant of these states are the pentavalent and the trivalent forms. In aqueous solutions, the pentavalent form occurs in the anion arsenate, $H_2AsO_4^-$. Arsenic lies directly below phosphorus in the periodic table, and, from structural and chemical points of view, arsenate is very similar to phosphate. The latter species plays several essential roles in the cell; it is a component of nucleic acids and lipids, regulates processes via phosphorylation of proteins, and transports energy within the cell via ATP. Because of its physico-chemical similarity to phosphate, arsenate, when available inside the cell, can compete with and substitute for phosphate in many reactions. This ability of arsenate raises questions about whether this substitution is harmful for the cell. If only partial substitution is possible, then the incorporation of arsenic instead of phosphorus is harmful. For example, if arsenic is incorporated in a reaction that is an early step (upstream) in a certain pathway but cannot function as phosphorus in a downstream reaction, then this pathway is disrupted. Previous research has demonstrated that the main toxicity of arsenate is due to its inhibition of the energy-linked reduction of NAD^+, mitochondrial respiration (citric acid cycle) and ATP synthesis. However, under normal environmental conditions, the intracellular levels of phosphate are sufficiently high that arsenate does not *directly* cause arsenic toxicity.

Given adequate modifications in the biochemistry of the cell, the possibility for arsenate to completely substitute for phosphorus to perform the vital processes of the cell has been questioned. Recent results suggest that the GFAJ-1 bacterium isolated from Mono Lake in eastern California is able to substitute arsenic for phosphorus to sustain its growth [13]. However, several scientists have commented that these results were misinterpreted [14]. The major concern is that arsenic esters are hydrolyzed rapidly and spontaneously in aqueous solutions; therefore, the stability of DNA, RNA, and sugar arsenates in aqueous environments would be too low to support life [15,16]. However, this life with arsenic instead of phosphorus is not possible for all other organisms, and in fact, when arsenic enters the cell, the pentavalent arsenate is reduced to the trivalent form.

Trivalent arsenic, or arsenite, which exists in aqueous solutions primarily as $As(OH)_3$ (the conjugate base is $As(OH)_4^-$ with a pK_a of 9.4), is more harmful than the pentavalent form and is responsible for the element's toxic effects. Its toxicity is primarily due to its propensity to form strong, nearly covalent bonds with closely spaced thiolates (cysteine residues) and imidazolium nitrogens (histidine), both of which are essential for the structure and function of proteins. As a consequence, the active sites of enzymes and receptors that contain cysteine residues can be inhibited, and the formation of disulfide bonds, needed to maintain a protein's tertiary structure, can be prevented. Many studies have shown that As(III) interacts with several important proteins. These proteins include cytoskeleton protein filaments (actin and tubulin), DNA repair proteins (PARP-1 and XPA), regulators of gene transcription (glucocorticoid receptor) and nicotinic receptors [17–21]. The binding of arsenic to these proteins likely involves the inactivation

of the proteins. For example, the binding of arsenic to tubulin prevents the tubulin's GTP-induced polymerization and lead to morphological transformation and some cytogenetic effects [19]. Another important consequence of the entry of As(III) into cells is the alterations in the methylation patterns of cellular DNA (both hypomethylation and hypermethylation were observed), which are normally observed in cancer cells [22,23]. In fact, chronic exposure to arsenic causes cancer of the liver, lung, skin, kidney and bladder [24]. For more than a decade, arsenic has been ranked as the most hazardous substance (http://www.atsdr.cdc.gov/cercla/97list.html). It also causes cardiovascular disease, peripheral neuropathies, and diabetes mellitus. Conversely, the binding of arsenic to proteins involved in intracellular signal transduction pathways results in the ability to use arsenic as a drug against cancer; for example, arsenic trioxide (Trisenox) is an effective chemotherapeutic agent for the treatment of acute promyelocytic leukemia [25].

Antimony is a trace element and typical concentrations in unpolluted systems are less than 1 μg/l [26,27]. Similar to arsenic, it can exist in four oxidation states, +5, +3, 0, and −3, with the pentavalent and the trivalent being the most abundant forms. Little is known about the biochemical effects of antimony; however, the working assumption is that its mode of action is similar to that of arsenic. It should be noted that this similarity in chemical properties has been assumed for many years without a rigorous study. In aqueous solutions, the trivalent form, antimonite, $Sb(OH)_3$, is isoelectronic to its arsenic counterpart, but the abundance of the conjugated anion, $Sb(OH)_4^-$, is smaller due to a higher acid dissociation constant ($pK_a = 11.7$). Despite the resemblance of trivalent antimony to trivalent arsenic, the pentavalent state of antimony in aqueous solutions is very different from the arsenate anion. In fact, the most abundant pentavalent form, antimonate, $Sb(OH)_6^-$ is a six-coordinated species [28]. Experimental and clinical trials with compounds containing antimony have demonstrated that the trivalent state is more toxic than the pentavalent state [29]. The primary effects of chronic exposure to antimony in humans are respiratory problems, lung damage, cardiovascular effects, gastrointestinal disorders, and adverse reproductive outcomes [30]. Similar to that of arsenic, the harmful effect of antimony on living systems can also be exploited in its use as a drug. Pentavalent antimony is a first-line treatment for leishmaniasis; however, to create the active form of the drug, the pentavalent antimony must first be reduced to the trivalent state.

2. Routes of transport of metalloids through the cell membrane

Transport is essential for maintaining life. This is because it is responsible for the uptake of vital substances from the environment and for the extrusion of unneeded and toxic compounds produced inside the cell. However, the mechanisms facilitating the uptake of vital elements can sometimes allow the undesired influx of toxic substances. In this case, another transport mechanism should operate to extrude the toxins out of the cell. At the molecular level, the cell membrane is primarily hydrophobic, inhibiting the transport of hydrophilic molecules. Although, small uncharged hydrophilic molecules, such as water, can diffuse directly through the lipid bilayer [31,32], larger hydrophilic molecules, such as sugars, cannot. The latter species require the use of specific transmembrane proteins to form a channel with an adequate hydrophilic environment to allow the molecules to cross from one side of the cell to the other.

As mentioned above, boron, silicon, arsenic, and antimony are metalloids that, in their most stable aqueous state, exist as multivalent poly-hydroxylated species. These compounds are hydrophilic and intermediate in size between the small molecules that can cross the cell membrane and the large molecules that require a channel protein for permeation. It is, therefore, not surprising that the route by which these metalloids enter the cell has been a subject of debate in the literature. Initially, it was thought that metalloids enter the cell only by passive unaided diffusion; however, there is now a wealth of evidence indicating that special integral membrane proteins facilitate the uptake/efflux of metalloids into/from the cell. The transport through these channels can be driven either by the difference in the concentration of the solute, where the direction of the diffusion is from high to low concentration (facilitated diffusion), or by energy-fueled pumps that can actively transport the solute against the concentration gradient. In the case of active transporters, energy in the form of ATP can be consumed directly by the transporter (primary active transporter) or by another ion-pumping protein, which transports Na^+ or H^+, that creates a difference in the electrochemical potential on both sides of the cell membrane. This difference in the electrochemical potential of sodium ions or protons is the driving force for the transport. Therefore, this type of transporters is known as secondary-active, and they normally transport ions. A way to distinguish between passive and active transport is to measure the transport activity as a function of solute concentration. A linear relationship indicates that the transport is passive (which can be accomplished either with or without channels). Alternatively, a curve that displays saturation indicates that the transport consumed energy (ATP) and is therefore active (which is accomplished by solute pumps). The latter behavior is reminiscent of the Michaelis Menten kinetics characteristic of enzymes.

Channels relevant to the passive transport of metalloids are aquaporins and aquaglyceroporins. These channels belong to the major intrinsic protein (MIP) superfamily of channel proteins found in all domains of life. Aquaporins selectively conduct water molecules, whereas aquaglyceroporins also transport other small uncharged molecules such as glycerol, carbon dioxide, ammonia and urea. However, almost all MIPs completely exclude the passage of ions and thereby preserve the electrochemical potential across the cell membrane. Both aquaporins and aquaglyceroporins are bi-directional channels that operate through passive diffusion. The direction of the transport is governed by the concentration gradient across the membrane. If the concentration of the solute inside the cell is too high and causes damage, the channel can facilitate the extrusion of the compound out of the cell if the extracellular concentration is lower. The overall structures of aquaporins and aquaglyceroporins are conserved [33–35]. Within the membrane, MIPs form tetramers, but each monomer constitutes a channel and is composed of six membrane-spanning helices. The selectivity of allowing or preventing the passage of a certain solute occurs at the channel's narrowest region, which permits only the single-file passage of molecules, that is, the molecules are transported one at a time. The polarity of the amino acids in this filter is believed to determine the selectivity. For example, in aquaglyceroporins, hydrophobic amino acids stabilize the hydrophobic backbone of glycerol, whereas polar amino acid residues hydrogen bond to the hydroxyl groups of glycerol [33,36]. The poly-hydroxylated forms of various metalloids are physically (in terms of size) and chemically (polarity and ability to form hydrogen bonds) similar to glycerol [37,38], rationalizing their ability to pass through certain MIPs [30,39].

The transport routes of boron, silicon, arsenic, and antimony into and out of the cell are reviewed below in details. Table 1 summarizes the transporters involved, and if known, the chemical species that is actually transported is indicated.

2.1. Transport of boron

If unaided passive diffusion of any of the metalloids occurs, then it is most likely to be observed for the smallest metalloid, which is boron. The uncharged boric acid is not only the most stable form of boron but also the state by which boron is transported into and out

Table 1
Summary of the different passive and active transporters of metalloids for permeation into (influx) and out (efflux) of the cell, and when known the species that is actually transported.

Transporter name	Direction	Metalloid transported[a]
Passive transport		
MIP: ZmPIP1, AtNIP5;1, HvPIP1;3, HvPIP1;4, NIP5;1, NIP6;1	Influx	Boron: $B(OH)_3$
MIP: Lsi1, HvLsi1, ZmNIP2-1, ZmNIP2-2, ZmNIP2-3	Influx	Silicon: $Si(OH)_4$ Arsenic: $As(OH)_3$, for Lsi1 also MMA(V), DMA(V)
MIP: Fps1, GlpF, AQP1	Influx	Arsenic: $As(OH)_3$ Antimony: $Sb(OH)_3$
MIP: NIP7;1	Influx	Arsenic: $As(OH)_3$
Glucose transporter: GLUT1 MIP: AQP7, AQP9	Influx	Arsenic: $As(OH)_3$, MMA(III)
MIP: AqpS, NIP2;1, NIP5;1, NIP6;1, NIP3;2	Influx & Efflux	Arsenic: $As(OH)_3$
Active transport		
unidentified	Efflux	Boron: $B(OH)_4^-$
SIT (sodium-coupled)	Influx	Silicon: likely in anionic form
Lsi2	Efflux	Silicon: likely in anionic form Arsenic: $As(OH)_4^-$
Phosphate transporters: -sodium-coupled: PiT-1, PiT2 -proton-coupled: Pho84, Pho87	Influx	Arsenic: $H_2AsO_4^-$
Acr3p (proton-coupled)	Efflux	Arsenic: assumed $As(OH)_3$ Antimony(III)
ArsB (proton-coupled)	Efflux	Arsenic(III) Antimony(III)
ABC transporters: Ycf1p, MRP2/cMOAT, PGPA, 190 kDa MRP	Efflux via extrusion into vacuoles	Arsenic(III)-thiol complex Antimony(III)-thiol complex

[a] MMA(V): mono-methylated As(V); DMA(V): di-methylated As(V); MMA(III): mono-methylated As(III).

of the cell. Therefore, it is a good candidate to have the proper solubility to cross the cell membrane without the aid of facilitators. Indeed, the passive diffusion of boron in different plants has been observed [40,41]. Nevertheless, active transport has also been proposed in other studies [42,43]. The passive transport of boron is reported to occur both with and without the aid of solute channel facilitators [44]. Few aquaporins and aquaglyceroporins have been demonstrated the ability to facilitate the uptake of boron in *Xenopus* oocytes [45–47] and in yeast [38]. The channels expressed in the oocytes were ZmPIP1 from maize and AtNIP5;1 from the flowering plant *Arabidopsis*. The channels expressed in yeast were HvPIP1;3 and HvPIP1;4 from barley roots. It appears that the extent of boron uptake by facilitated diffusion via these transporters account for approximately 25–50% of the total boron uptake. The NIP5;1 and NIP6;1 channels were also shown to facilitate the permeation of boric acid in *Arabidopsis* [48]. As for the active transport, no specific solute pumps have been identified. Such an energy-consuming mechanism is assumed to be utilized under deficiency conditions because the uptake can still be performed, albeit at lower extracellular concentrations. It should be mentioned that in addition to facilitated uptake of metalloids into the cell, the efflux out of the cell is also facilitated by protein channels. This facilitated efflux has been demonstrated to provide plants with tolerance against high concentrations of boron, which can be toxic [49]. The efflux is found to be an active transport, where boron is transported in the form of $B(OH)_4^-$. Note that although the concentration of the anion is small compared to that of $B(OH)_3$, its continuous disappearance in the intracellular medium can consume a large quantity of the neutral species because the equilibrium reaction between the two species will be shifted to produce more anions.

2.2. Transport of silicon

All living organisms are able to take up silicon, and similar to boron, silicon is taken up in its uncharged hydroxylated form, $Si(OH)_4$ [50]. The gene responsible for silicon uptake in rice is low silicon rice 1 (Lsi1) and encodes a plasma membrane protein that belongs to the Nodulin26-like intrinsic proteins (NIP) subfamily of aquaporins [9]. This protein channel, which was also observed in barley [51], does not transport glycerol to any significant extent. The gene is constitutively expressed, but its expression level is regulated by the extracellular concentration of silicon. A homologous protein, HvLsi1, that belong to the same subgroup of aquaporins was also found to facilitate the influx of silicic acid in barley [51], and three other homologues were also found in maize (ZmNIP2-1, ZmNIP2-2 and ZmNIP2-3), suggesting that they are also involved in silicon uptake. The location of Lsi1 expression is mainly in the roots, and there is a need for the silicon accumulated in these cells to be transported to cells in other locations. In addition to channels that allow influx, this intercellular transport also requires a mechanism that will permit the efflux of silicon. As mentioned above, aquaporins are mostly bidirectional for water transport; however, measurements demonstrated that Lsi1 does not transport silicon out of the cell. This finding is in contrast to other NIP aquaporins that are bidirectional for arsenic [52]. Another gene, low silicon rice 2 (Lsi2), encodes for another plasma membrane protein that is responsible for silicon efflux [53]. Lsi2 is also constitutively expressed in the roots but has no similarity to Lsi1 and does not facilitate any uptake of silicon. In fact, there are some indications suggesting that Lsi2 is a putative anion transporter and is energetically driven by a proton gradient. Thus, whereas the influx of silicon into the cell is accomplished passively via diffusion, the efflux is an active process.

In contrast to the passive influx and active efflux examples mentioned above, marine diatoms are able to take up silicon, via

Table 2
Reported nanosilica mammalian cellular uptake mechanisms.

Silica form[a]	Size (nm)	Zeta-potential[b] (mV)	Cells[c]	Mechanism[d]	Method[e]	Refs.
FITC-MSN	~110	–	hMCSs, 3T3-L1	Clathrin-mediated endocytosis	Inhibitors (sucrose, phenylarsine oxide, filipin)	[126]
MSN: MCM-41 type, functionalized: – FITC – AP – GP – GEGP – FAP	150 (pore ∅ ~ 2.4)	 −34.73 −4.68 −3.25 +0.57 +12.81 (pH 7.4)	HeLa	Endocytosis: – FITC: clathrin-pitted mechanism mediated by folic acid receptors – FAP: clathrin-pitted mechanism non-mediated by folic acid receptors – AP and GP: caveolar-mediated mechanism – GEGP: (unknown)	Inhibitors (sucrose, folic acid, genistein)	[127]
RITC-MSN, surface modified with variable amounts of positively charged TMAC	108 110 111 115	+19.0 +14.6 +7.90 −4.90 (pH 7.35)	hMCSs, 3T3-L1	hMSCs: – low surface charge: clathrin and actin-dependent endocytosis – above a charge threshold: new unrevealed charge-dependent mechanism 3T3-L1: - clathrin-dependent mechanism, charge independent	Inhibitors (phenylarsine oxide, filipin, cytochalasin D, nocodazole)	[128]
FITC-iron oxide/silica core-shell particles	50 (core: 10)	–	hMSCs	Clathrin-coated pit endocytosis and actin microfilaments involved	Inhibitors (phenylarsine oxide, cytochalasin D, filipin, nocodazole)	[129]
Aminated amorphous particles	92, 462	+20 (pH 7.4)	C10	Particles propelled along microvilli-like structures into cells	Identification of individual particles by DIC (500 nm) or TIRF (100) microscopy	[130]
MSN, surfactant (CTAB) extracted or calcinated	190, 420, 1220	Negative (in figure), increase with size	MDA-MB-468, COS-7	Endocytosis; size dependent	Located in lysosomes (confocal microscopy)	[131]
Gd-FITC-MSN	120	–	hMSCs	Clathrin-coated pit endocytosis and actin microfilaments involved	Inhibitors (phenylarsine oxide, cytochalasin D, filipin, wortmannin, nocodazole)	[132]
Aminated amorphous particles	462	+20 (pH 7.4)	C10	Syndecan-1 mediates particle coupling with actin filaments across the membrane and internalization via macropinocytosis	Flow-cytometry and enzyme treatments, TIRF, FCM	[133]
FITC-AMS	MS6: 378 (pore ∅ 3.43), AMS8: 2400	–	HMDM	Energy-dependent internalization; endocytosis and phagocytosis implicated; impossible to clarify whether clathrin- or caveolae-mediated endocytosis involved	Reduced uptake at low T incubation, inhibitors (cytochalasin D and a "cocktail of endocytosis inhibitors")	[134]
Amorphous particles, dyed (fluorescent dansylamide)	150–200	−23 (pH not given)	Rat microglia	Phagocytosis; concentration dependent: – lower concentrations, dispersed in cytoplasm – higher concentrations, in phagocytic vacuoles	FCM	[135]
Core-shell silica particles encapsulating fluo dye with hydroxyl, aminopropyl, PEGylated surface modifications	200–300	–OH: −40, $–NH_2$: +11.3, −PEG: +4.29	UMB-SCC-745	PEG: no intake Others: – single particles: membrane invaginations resembling clathrin-coated pits – clusters: membrane ruffling (probably macropinocytosis)	TEM	[136]
Amorphous particles, FITC or RITC doped, sorption of serum proteins possible	60, 178, 369, 592	Negative in DMEM medium, decreased in DMEM/10% FBS medium	HepG2	Clathrin-dependent endocytosis	Reduced uptake at low T incubation, inhibitors (NaN3, sucrose, amandatine-HCl)	[125]
Amorphous particles, fluorescent (red-F)-labeled	70, 300, 1000	–	HaCaT	– 70 nm: actin-mediated endocytosis, such as macropinocytosis; – >70 nm: markedly reduced response	Cytochalasin D-treatment reduced 70 nm-mediated ROS generation and DNA damage	[137]

(*continued on next page*)

Table 2 (*continued*)

Silica form[a]	Size (nm)	Zeta-potential[b] (mV)	Cells[c]	Mechanism[d]	Method[e]	Refs.
Amorphous (precipitated, anionic) particles, dyed (Alexa 546 and 488) but low covering, serum-free medium	100	-Parent: −38.2; -546: −42.3; -488: −37.0	RAW 264.7 HEK-293 with introduced SR-A expression	– Clathrin-dependent endocytosis, SR-A mediated – Agglomerated >500 nm, poorly co-localised with the receptor	Co-localization with SR-A and transferrin (FCM) and inhibition by K depletion	[138]

[a] AMS: anionic templated mesoporous solid; AP: 3-aminopropyl; FAP: N-folate-3-aminopropyl; CTAB: cetyltrimethyl ammonium bromide; FITC: fluorescein isothiocyanate; GEGP: 3-[*N*-(2-guanidinoethyl)guanidino]propyl; GP: guanidinopropyl; MSN: mesoporous silica nanoparticle; RITC: rhodamine B isothiocyanate; TMAC: trimethoxysilylpropyl-*N*,*N*,*N*-trimethylammonium chloride.

[b] DMEM: Dulbecco's modified Eagle's medium; FBS: fetal bovine serum.

[c] 3T3-L1: mouse embryonic cells; C10: alveloar type II epithelial cell line; COS-7: African green monkey kidney cells; HaCaT: human keratinocyte cell line; HEK-203: human cells; HeLa: human cervical cancer cells; HepG2: human liver cancer cells; HMDM: primary human monocyte-derived macrophages; hMSCs: human esenchymal stem cells from bone marrow; MDA-MB-468: human breast cancer cells; RAW 264.7: murine macrophage cell line; UMB-SCC-745: human head and neck squamous carcinoma cell line.

[d] SR-A: scavenging receptor A.

[e] DIC: time-lapse differential interference contrast; FCM: fluorescence confocal microscopy; ROS: reactive oxygen species; SR-A: scavenging receptor A; TEM: transmission electron microscopy; TIRF: time-lapse total internal reflection fluorescence laser microscope.

silicon transporters known as SITs, by an active mechanism [54]. These algae use silica as a material to build their cell wall. However, in contrast to Lsi1, the Si channel in these algae is active and requires sodium ions [55]. Furthermore, the SIT pump has no resemblance to Lsi2, despite the fact that both are energy-dependent silicon transporters.

2.3. Uptake and reduction of pentavalent arsenic and antimony

Because the dominant species of pentavalent arsenic in aqueous solution, $H_2AsO_4^-$, is isoelectronic and similar in volume to phosphate, $H_2PO_4^-$, phosphate transporters can potentially allow the passage of arsenate. This situation is probably true in most organisms including humans [56]. For example, in the prokaryote *Escherichia coli*, the phosphate transporters PiT-1 and PiT-2 have been shown to facilitate arsenate uptake [57,58]. Both channels are secondary-active, sodium-coupled transporters. In the eukaryotic yeast *Saccharomyces cerevisiae*, arsenate was shown to enter the cell through two phosphate transporters, Pho84 and Pho87 [59,60]. The former protein is known to catalyze this uptake by a proton-coupled mechanism under acidic conditions. Other evidence of arsenate uptake through phosphate transporters in plants is provided by Bienert and Jahn [61]. In each of these cases, the transport that occurs is an influx into the cell, and the deletion of the genes encoding for the phosphate transporters provided the organism with resistance against high extracellular concentrations of arsenate. Nevertheless, this transport is not how biology evolved to cope with arsenic toxicity.

Upon its entry into the cell, arsenate is reduced to the trivalent arsenite. Four families of arsenate reductases have been identified to date [62]. Two families, represented by ArsC from *S. aureus* plasmid pI258 and Acr2p from *S. cerevisiae*, are structurally related to two different tyrosine phosphate phosphatases and exhibit low phosphatase activities [63–65]. The sources of the reducing agents are thiol-based molecules: the redox protein thioredoxin for pI258 ArsC and glutathione/glutaredoxin for Acr2p. The third family is represented by ArsC from *E. coli* plasmid R773, an enzyme with no structural elements in common with phosphatases [66]. In this case, the source of the electron donor is glutathione or glutaredoxin. The crystal structures of pI258 ArsC [67] and R773 ArsC [68] contributed to the current understanding of the mechanisms of the reactions. A fourth family of arsenate reductase was discovered in *Chrysiogenes arsenatis* [69]. In this case, the enzyme, Arr, has no similarities to phosphatases, but it is still distinct from R773 ArsC as implied by the fact that it uses acetate as the source of the electron donor molecule. The reduction of arsenate to arsenite has also been observed in mammals [70]; however, no enzyme has been identified yet.

As mentioned above, trivalent arsenic is more toxic than the pentavalent state. This finding raises questions concerning why a cell would develop mechanisms to reduce arsenate to arsenite, thus, increasing the toxicity of the element inside the cell. Rosen [71] argues that this reduction is because the cell, in the course of evolution, was forced to first develop channels to extrude trivalent arsenite. The reason for this efflux is that the primordial atmosphere was not oxidizing, and therefore, most arsenic was in the form of As(III). Only when the atmosphere became oxidizing did arsenic in the form of arsenate appear. However, instead of developing a new route of transport for arsenate efflux, it was easier to convert phosphate reductases to arsenate reductases and allow the resulting product, arsenite, to exit the cell through existing channels.

In contrast to arsenate, the entrance route of pentavalent antimony, or antimonate, into the cells has not yet been identified. The uptake mechanism may be different from that of arsenate because the stable form of antimonate in aqueous solutions, $Sb(OH)_6^-$, is not isoelectronic with arsenate/phosphate. Nevertheless, once antimonate is inside the cell, it is also reduced to the trivalent state, antimonite. The only antimonate reductase known to date is LmACR2 from *Leishmania major*. This enzyme also reduces arsenate and phosphate [72,73], unlike the arsenate reductases that are selective to As(V) and do not reduce Sb(V). The three-dimensional structure of LmACR2 was obtained by X-ray crystallography [62], and it displays sequence and functional similarity with the arsenate reductase Acr2p. Accordingly, LmACR2 uses glutathione as the reducing agent [74]. Although the enzyme reduces Sb(V) faster than As(V) or phosphate, its physiological function is actually proposed to be the dephosphorylation of phosphotyrosine residues [73]. The process of reducing antimonate to antimonite is very important because, as is the case for arsenic, the trivalent form of antimony is the active and the more toxic state. Thus, because the pentavalent state of antimony is used in drugs for the treatment of leishmaniasis, it first has to be reduced to the trivalent state to be effective [75,76]. Furthermore, antimonite appears to be the state in which antimony is extruded from the cell.

2.4. Uptake and efflux of trivalent arsenic and antimony

The transport of arsenite and antimonite into and out of the cell can be conducted passively or actively. The channels facilitating the passive routes belong to the NIP subgroup of aquaglyceroporins [77]. The glycerol channel Fps1 from the yeast *S. cerevisiae*

[78] and GlpF from the bacteria *E. coli* [79] were demonstrated to mediate the uptake of As(III) and Sb(III) into the cell. In the latter case, the deletion of the encoding gene accounted for a 90% reduction in arsenite uptake [80]. In plants, arsenite uptake was demonstrated to involve the NIP7;1 from *Arabidopsis* [81]. Another aquaglyceroporin that transports $As(OH)_3$ is the human AQP9. This transport has been demonstrated when the channel was expressed in *X. laevis* oocytes [82]. Furthermore, it has been shown that AQP9 overexpression in leukemic cells sensitizes the cells to As(III) [83–85]. The increased sensitivity was due to higher rates of arsenite uptake. AQP7 also transports As(III) but to a much lesser extent than AQP9 does. Additionally, AQP1 can facilitate transport of antimonite and arsenite in several *Leishmania* species [86–88]. There are 13 known types of human aquaporins in mammals. AQP9 has the broadest specificity and is able to transport water, glycerol, urea, carbamides, polyols, purines, and other compounds; thus, it is not surprising that it is the most efficient aquaporin channel for the uptake of metalloids. To explore the selectivity of AQP9 to transport glycerol vs. arsenic trioxide, the role of specific residues in the permeability of both molecules was examined by site-directed mutagenesis [89]. The mutations performed had the same effect on the uptake of glycerol as on the uptake of arsenite, which demonstrates that the transport of the latter species is a result of its physico-chemical similarity to glycerol [37].

Although MIPs are bidirectional, in most of these studies the aquaglyceroporin channels were observed to preferentially facilitate uptake over efflux of arsenite and antimonite. However, Yang et al. [90] found that the aquaglyceroporin AqpS from *S. meliloti* plays an important role in arsenic detoxification by facilitating the efflux of arsenite out of the cell. Other examples of bidirectional arsenic channels were also found within the NIP subgroup of aquaglyceroporins in plants. In particular, NIP5;1 and NIP6:1 from *A. thaliana* and *L. japonicus* and NIP2;1 and NIP3;2 from *O. sativa* were shown to transport arsenite into and out of the cell [52]. Some of these NIP channels are also known to transport the essential/beneficial metalloids boron and silicon, and it is tempting to speculate that these channels were evolved for the uptake of these metalloids. Nevertheless, no selectivity in the uptake of these metalloids relative to As(III) was detected [52]. Furthermore, the characteristics of arsenite transport in rice grains were found to be very similar to those of silicic acid transport. In particular, the Lsi1 transporter, which is also an NIP aquaglyceroporin, has been shown to mediate the uptake of arsenite from the external medium, whereas the Lsi2 transporter has been shown to mediate the efflux of arsenite, allowing intercellular transport [91]. Another type of channel involved in the uptake of arsenite is GLUT1 which is a glucose transporter that also functions via facilitated diffusion [92].

The passive diffusion of arsenite and antimonite through the cell membrane is not the only transport route that exists. Primary- and secondary-active transporters have also been discovered. An example of the latter transporter is the route of arsenic detoxification discovered in the yeast *S. cerevisiae*. This mechanism, which is conserved from bacteria to plants, has been shown to involve a cluster of three genes: ACR1, ACR2, and ACR3 [60,64,93,94]. ACR1 is a regulatory gene whose inactivation results in sensitivity to arsenate and arsenite. The protein encoded by ACR2, Acr2p, is the arsenic reductase mentioned above. The product of this reductase, As(III), is then extruded out of the cell by Acr3p, a plasma membrane protein encoded by ACR3. For a long time, the energy requirements and kinetics of the efflux of As(III) by Acr3p were not known. However, it was demonstrated recently that this efflux is coupled to the electrochemical potential gradient of protons generated by the plasma membrane H^+-ATPase [95]. The species that is actually transported is believed to be the neutral hydroxylated arsenite, $As(OH)_3$. The fact that these three genes are under the control of a single regulatory promoter suggests that the Acr3p evolved specifically to extrude arsenite out of the cell. In addition to arsenite, the transport of antimonite via Acr3p has also been demonstrated [95].

Another example of an energy-consuming transporter, which is found in bacteria and archaea but absent in eukaryotes, is represented by the ArsB carrier protein [66,96,97]. This integral membrane protein has been shown to catalyze the efflux of arsenite and antimonite and, therefore, provide resistance against the toxic effects of these species. ArsB forms a complex with the catalytic subunit ArsA and displays ATP-dependent activity. The efflux of As(III) and Sb(III) is then coupled to an electrochemical gradient via proton exchange [80].

It has also been observed that resistance to arsenic and antimony can be obtained through the ATP-binding cassette (ABC) transporters [98]. These membrane proteins transport a wide range of substrates, such as, ions, phospholipids, steroids, polysaccharides, amino acids, peptides, and conjugated organic anions. One member of the family in the yeast *S. cerevisiae*, Ycf1p, operates against arsenite and antimonite toxicity by transporting these species into vacuoles (intracellular organelles), which are then exported out of the cell [94]. Another example is the extrusion of arsenic from the liver into the bile via the MRP2/cMOAT transporter [99]. These translocations via ABC transporters require the complexation of the metalloid with a thiol-based molecule such as glutathione. The species that is actually transported is the metalloid-thiol adduct, predominantly in the form of arsenic triglutathione and methylarsenic diglutathione [99,100].

Due to their toxicity, compounds of arsenic and antimony can also serve as drugs. However, if a detoxification mechanism is operational in the drug target cell (for example, the parasite), then a resistance against the metalloid's curing effect can be developed. This is a general phenomenon that is not restricted to the use of metalloids as drugs, and accordingly, these ABC transporters have been named multidrug resistance proteins (MRP) [101]. Resistance against arsenic and antimony has been observed in *Leishmania* [100,102] due to the PGPA transporter and in human cancer cells due to P-glycoprotein and a 190 kDa MRP transporter [103,104]. In both cases, the overexpression of these ABC transporters provided the resistance against the drug [102,105–107].

Similarly, the strong affinity between arsenite/antimonite and sulfhydryl groups is exploited extensively by plants to neutralize the harmful effects of these metalloids by forming complexes with phytochelatins (PCs) [108]. PCs are thiolate peptides that are synthesized non-translationally from the related tripeptide glutathione by the phytochelatin synthase [109]. The metalloid-thiol complexes are then transported for vacuolar sequestration [110,111].

2.5. Transport of methylated arsenic

Although similar to glycerol, the hydroxylated metalloids do not have the nonpolar methyl groups of glycerol and, thus, are probably less hydrophobic. Can the toxicological properties of the metalloid change upon increasing the hydrophobicity of the metalloid? A group of enzymes belonging to the family of S-adenosylmethyltransferases are known to catalyze the substitution of the hydroxyl groups with methyl groups in arsenite and antimonite. The biomethylation of arsenic has been widely observed in some organisms including humans, and it plays an important role in the detoxification of As(III) [112]. In contrast, the biomethylation of antimony was discovered much later, and it appears that antimony can be methylated much less rapidly and less extensively than arsenic can [113]. In most cases, the methylation of antimony is due to bacterial or fungal activity [114–116]. Different levels of methylation have been observed, including mono-, di-, and tri-

methylated metalloids. In fact, the tri-methylated species, which is a non-toxic gas, is believed to be sufficiently hydrophobic to pass through biological membranes without the need of special channels. Nevertheless, the mono-methylated metalloid accounts for a large proportion of the total quantity of the metalloid in the cell. In this case, the aid of a channel is needed. The mammalian aquaglyceroporins AQP7 and AQP9 and the glucose transporter GLUT1 have been shown to facilitated the uptake of mono-methylated trivalent arsenite [92,117]. The rate of this transport was approximately three times faster for the methylated compound compared to the unmethylated compound. In mammals, the methylation occurs primarily in the liver, and the products are excreted into the bile and urine. However, the efflux mechanism of the methylated species is not known. The methylation of arsenite in higher plants has not yet been recorded. Notwithstanding, the gene encoding the bacterial arsenite methyltransferase was integrated in the Japonica rice genome and was able to express the corresponding methyltransferase enzyme [118]. When exposed to trivalent or pentavalent arsenic, the transgenic rice produced both mono-methylated and di-methylated arsenate that evolved volatile arsenicals. It is interesting to note that the rice aquaporin Lsi1 was observed to mediate the uptake of mono- and di-methylated pentavalent arsenic in rice roots [119].

3. Routes of transport of nano-sized metalloids

The routes for the transport of metalloids into cells discussed in previous sections concern the so-called 'dissolved' elements. In this case, the only way the metalloids can enter the cell is via crossing the cell membrane either with or without the aid of channels. However, when these elements form or are embedded in nano-sized particles, they can gain entry into the cell by the process of endocytosis without passing through the cell membrane. In this mechanism, the cell membrane can engulf the nano-sized particles and invaginate them into the cell by forming an intracellular vesicle.

Although many elements are naturally present in nano-sized materials, the current boost in research into the behavior of such materials in living systems is linked to the recent development of nanotechnology. The nanosciences have grown exponentially over the past decade as advances in synthesis techniques have made manufacturing nano-materials increasingly straightforward and accessible. Although there is no consensus on their definition, it is generally accepted that nano-particles are engineered structures that have at least one dimension of 100 nanometers or less and that show novel size-dependent properties (i.e., differing from those of bulk materials of the same composition).

Boron-, antimony- and, primarily, silicon-containing compounds in the nano-size range are either produced and used commercially or the subject of developments in current research. Boron-containing nanoparticles can be found in a wide variety of applications, including special purpose alloys, lubricant additives, neutron-detecting devices, nuclear reactor controls, oxygen scavengers, pharmaceutical and medical industries, pyrotechnic flares, rocket-propellant mixtures, semi-conductor dopant coatings and micro-coatings for precision cutting tools, aerospace coatings, and plastics. Antimony and its compounds are and have been used in a variety of products. Major antimony compounds are antimony oxides, chlorides and sulfides, and their main non-metal applications include catalysis in the production of thermoplastics, in lubricants (e.g., brake pads), glass, ceramics, and as flame retardants. In most of these applications, antimony compounds in the micron-size range are used; nevertheless, nano-sized compounds are increasingly being utilized because they present advantages, such as providing low-tint polymers, better translucency or the possibility of producing flame-retardant fine denier fibers and monofilaments. However, of the elements considered in this review, silica nanoparticles are the most widely produced and used. Silica is the common name for materials composed of silicon dioxide, and it occurs in crystalline and amorphous forms. Silica also includes mesoporous materials with well-defined and tunable pore sizes. According to the nanotechnology inventory of the Woodrow Wilson Project on Emerging Nanotechnologies (www.nanotechproject.org), silica is the fourth most used nanomaterial in commercial applications. Silica nanoparticles are produced on an industrial scale as additives to cosmetics, drugs, printer toners, varnishes and food. In addition, nanosilica is being developed for a host of biomedical and biotechnological applications such as cancer therapy and drug delivery. The physicochemical properties and applications of the different types of silica materials have been discussed recently [120,121].

Very few studies have been devoted to the toxicology of boron and antimony nano-compounds, and virtually no studies have followed their uptake by cells. In contrast, several in vitro studies have been conducted to examine nano-silica particle toxicity and uptake, primarily concerning mammalian cells including human cancer cells. Nano-particle uptake is often followed by the coupling of nano-particles to a fluorophore and the fluorescence tracking of treated cells using fluorescence confocal microscopy (FCM). Alternatively, particles in cells can be detected with transmission electron microscopy (TEM). These techniques have made it possible to observe amorphous silica nano-particle internalization and accumulation in the cytoplasm and the nucleus [120,122].

As mentioned above, the main route by which cells absorb macromolecules or nano-particles is endocytosis. This process includes phagocytosis, a term usually used to describe the uptake of particulate materials larger than 0.5 μm; macropinocytosis; endocytosis that is dependent on the coat proteins clathrin or caveolin; and endocytosis that is independent of clathrin and/or caveolin. The current knowledge on the subject and the methods used in this field have recently been critically evaluated [123]. We summarize in Table 2 the observed uptake mechanisms for nano-silica in the different experimental setups used. Clathrin-mediated endocytosis appears to be the most common mechanism reported to date. However, this conclusion and its generalization should be taken with caution because the mechanisms of cellular uptake depend on parameters such as particle size (e.g., isolated nano-particles and aggregates appear to use different internalization mechanisms), surface charge, surface modification, dose, test media (e.g., the presence or absence of proteins), exposure time or cell type used as a model. In particular, some issues that need to be considered when evaluating the results in Table 2 include the following: (i) the probable need to re-interpret the data in light of recent studies [123]; (ii) the fact that most of the particles in Table 2 are not in the nano-size range, which means that, because size is a key parameter in both total uptake [124] and uptake mechanisms, the uptake pathways in Table 2 may not apply to 'real' nano-particles; and (iii) the importance of particle surface functionalization. Although it is common practice in most study titles to mention only the name of the inorganic particle (e.g., 'silica'), this practice is misleading; most of the nano-particles in Table 2 and in real life applications are not 'naked' silica but are particles with modified surfaces. Because most of the main properties of nano-particles are strongly surface dependent (e.g., charge, aggregation, binding), the observed behavior may, in some cases, be more dependent on the type of functionalization than on the underlying material.

The fate of nanoparticles after mammalian cellular uptake has been less studied. One possible fate is exocytosis, which was postulated for FITC-SiO2 nano-particles in HepG2 cells [125]. It was observed that exocytosis was size dependent, with larger particles being harder to exocytose.

4. Conclusions

From the evidence collected to date, it appears that only boron compounds are able to pass through the cell membrane directly without the aid of facilitators. Nevertheless, a substantial portion of this metalloid uptake is performed by aquaglyceroporin-facilitated diffusion. In contrast, the facilitated efflux of the corresponding hydrated ions requires energy. Conceptually, similar mechanisms of passive (facilitated by aquaglyceroporin) influx and active efflux have been observed for silicon in rice. However, the generalization of these schemes is hampered by the active uptake route exhibited by marine diatoms. The uptake of toxic trivalent arsenic and antimony species is performed passively via different MIPs that have evolved for the uptake of different compounds. Extrusion is an active process, and the Acr3p transporter, at least, has evolved for arsenite detoxification. Again, the generalization for passive influx and active efflux is prohibited due to passive extrusion through the AqpS aquaglyceroporin. Furthermore, the affinity of As(III) and Sb(III) for sulfhydryl groups is utilized for the formation of metalloid-thiol complexes that are sequestered into vacuoles by ABC transporters. To augment the efficiency of arsenite and antimonite for passive extrusion, these compounds can be methylated to increase their hydrophobic character. In contrast to these routes of transport, the need to pass through the cell membrane to enter the cell can be avoided if these metalloids form or are incorporated into nano-sized particles. Different mechanisms of endocytosis in mammalian cells have been reported for the case of silica.

Conflicts of Interest statement

The authors declare that there are no conflicts of interest.

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References

[1] D.G. Blevins, K.M. Lukaszewski, Boron in plant structure and function, Annu. Rev. Plant Physiol. Plant Mol. Biol. 49 (1998) 481–500.
[2] P.H. Brown, N. Bellaloui, M.A. Wimmer, E.S. Bassil, J. Ruiz, H. Hu, H. Pfeffer, F. Dannel, V. Römheld, Boron in plant biology, Plant Biol. 4 (2002) 205–223.
[3] L. Bolaños, K. Lukaszewski, I. Bonilla, D. Blevins, Why boron?, Plant Physiol Biochem. 42 (2004) 907–912.
[4] F.H. Nielsen, Evidence for the nutritional essentiality of boron, J. Trace Elem. Exp. Med. 9 (1996) 215–229.
[5] F.H. Nielsen, J.G. Penland, Boron supplementation of peri-menopausal women affects boron metabolism and indices associated with macromineral metabolism, hormonal status and immune function, J. Trace Elem. Exp. Med. 12 (1999) 251–261.
[6] N.K. Savant, G.H. Snyder, L.E. Datnoff, Silicon management and sustainable rice production, Adv. Agron 58 (1997) 151–199.
[7] E. Epstein, The anomaly of silicon in plant biology, Proc. Natl. Acad. Sci. USA 91 (1994) 11–17.
[8] K.E. Richmond, M. Sussman, Got silicon? The non-essential beneficial plant nutrient, Curr. Opin. Plant Biol. 6 (2003) 268–272.
[9] J.F. Ma, K. Tamai, N. Yamaji, N. Mitani, S. Konishi, M. Katsuhara, M. Ishiguro, Y. Murata, M. Yano, A silicon transporter in rice, Nature 440 (2006) 688–691.
[10] E. Epstein, Chapter 1 silicon in plants: facts vs. concepts, in: G.H.S.L.E. Datnoff, G.H. Korndörfer (Eds.), Silicon in agriculture, Studies in Plant Science, vol. 8, Elsevier, Amsterdam, 2001, pp. 1–15.
[11] A. Lassus, Colloidal silicic acid for oral and topical treatment of aged skin, fragile hair and brittle nails in females, J. Int. Med. Res. 21 (1993) 209–215.
[12] A. Barel, M. Calomme, A. Timchenko, K.D. Paepe, N. Demeester, V. Rogiers, P. Clarys, D.V. Berghe, Effect of oral intake of choline-stabilized orthosilicic acid on skin, nails and hair in women with photodamaged skin, Arch. Dermatol. Res. 297 (2005) 147–153.
[13] F. Wolfe-Simon, J.S. Blum, T.R. Kulp, G.W. Gordon, S.E. Hoeft, J. Pett-Ridge, J.F. Stolz, S.M. Webb, P.K. Weber, P.C.W. Davies, A.D. Anbar, R.S. Oremland, A bacterium that can grow by using arsenic instead of phosphorus, Science (doi: 10.1126/science.1197258).
[14] E.C. Hayden, Will you take the 'arsenic-life' test?, Nature 474 (2011) 19
[15] B.P. Rosen, A.A. Ajees, T.R. McDermott, Life and death with arsenic, BioEssays 33 (2011) 350–357.
[16] S.A. Benner, Comment on a bacterium that can grow by using arsenic instead of phosphorus, Science 322 (2011) 1149.
[17] R.D. Hoffman, M.D. Lane, Iodophenylarsine oxide and arsenical affinity chromatography: new probes for dithiol proteins, J. Biol. Chem. 267 (1992) 14005–14011.
[18] D.B. Menzel, H.K. Hamadeh, E. Lee, D.M. Meacher, V. Said, R.E. Rasmussen, H. Greene, R.N. Roth, Arsenic binding proteins from human lymphoblastoid cells, Toxicol. Lett. 105 (1999) 89–101.
[19] Y.M. Li, J.D. Broome, Arsenic targets tubulins to induce apoptosis in myeloid leukemia cells, Cancer Res. 59 (1999) 776–780.
[20] X. Zhang, F. Yang, J.-Y. Shim, K.L. Kirk, D.E. Anderson, X. Chen, Identification of arsenic-binding proteins in human breast cancer cells, Cancer Lett. 255 (2007) 95–106.
[21] K.T. Kitchin, K. Wallace, The role of protein binding of trivalent arsenicals in arsenic carcinogenesis and toxicity, Cancer Lett. 102 (2008) 532–539.
[22] C.X. Zhong, M.J. Mass, Both hypomethylation and hypermethylation of DNA associated with arsenite exposure in cultures of human cells identified by methylation-sensitive arbitrarily-primed PCR, Toxicol. Lett. 122 (2001) 223–234.
[23] H. Chen, S. Li, J. Liu, B.A. Diwan, J.C. Barrett, M.P. Waalkes, Chronic inorganic arsenic exposure induces hepatic global and individual gene hypomethylation: implications for arsenic hepatocarcinogenesis, Carcinogenesis 25 (2004) 1779–1786.
[24] P.B. Tchounwou, A.K. Patlolla, J.A. Centeno, Carcinogenic and systemic health effects associated with arsenic exposure – a critical review, Toxicol. Pathol. 31 (2003) 575–588.
[25] Z.-X. Shen, G.-Q. Chen, J.-H. Ni, X.-S. Li, S.-M. Xiong, Q.-Y. Qiu, J. Zhu, W. Tang, G.-L. Sun, K.-Q. Yang, Y. Chen, L. Zhou, Z.-W. Fang, Y.-T. Wang, J. Ma, P. Zhang, T.-D. Zhang, S.-J. Chen, Z. Chen, Z.-Y. Wang, Use of arsenic trioxide (As_2O_3) in the treatment of acute promyelocytic leukemia (APL): II. Clinical efficacy and pharmacokinetics in relapsed patients, Blood 89 (1997) 3354–3360.
[26] M. Filella, N. Belzile, Y.-W. Chen, Antimony in the environment: a review focused on natural waters: I. Occurrence, Earth-Sci. Rev. 57 (2002) 125–176.
[27] M. Filella, P.A. Williams, N. Belzile, Antimony in the environment: knowns and unknowns, Environ. Chem. 6 (2009) 95–105.
[28] M. Filella, N. Belzile, Y.-W. Chen, Antimony in the environment: a review focused on natural waters: II. Relevant solution chemistry, Earth-Sci. Rev. 59 (2002) 265–285.
[29] T. Gebel, Arsenic and antimony: comparative approach on mechanistic toxicology, Chem.-Biol. Interact. 107 (1997) 131–144.
[30] H. Bhattacharjee, B.P. Rosen, R. Mukhopadhyay, Aquaglyceroporins and metalloid transport: implications in human diseases, Handb. Exp. Pharmacol. 190 (2009) 309–325.
[31] D.W. Deamer, J. Bramhall, Permeability of lipid bilayers to water and ionic solutes, Chem. Phys. Lipids 40 (1986) 167–188.
[32] M. Jansen, A. Blume, A comparative study of diffusive and osmotic water permeation across bilayers composed of phospholipids with different head groups and fatty acyl chains, Biophys. J. 68 (1995) 997–1008.
[33] D. Fu, A. Libson, L.J.W. Miercke, C. Weitzman, P. Nollert, J. Krucinski, R.M. Stroud, Structure of a glycerol-conducting channel and the basis for its selectivity, Science 290 (2000) 481–486.
[34] K. Murata, K. Mitsuoka, T. Hirai, T. Walz, P. Agre, J.B. Heymann, A. Engel, Y. Fujiyoshi, Structural determinants of water permeation through aquaporin-1, Nature 407 (2000) 599–605.
[35] C. Maurel, Plant aquaporins: novel functions and regulation properties, FEBS Lett. 581 (2007) 2227–2236.
[36] M.Ø. Jensen, E. Tajkhorshid, K. Schulten, The mechanism of glycerol conduction in aquaglyceroporins, Structure 9 (2001) 1083–1093.
[37] A. Porquet, M. Filella, Structural evidence of the similarity of $Sb(OH)_3$ and $As(OH)_3$ with glycerol: implications for their uptake, Chem. Res. Toxicol. 20 (2007) 1269–1276.
[38] K.L. Fitzpatrick, R.J. Reid, The involvement of aquaglyceroporins in transport of boron in barley roots, Plant Cell Environ. 32 (2009) 1357–1365.
[39] G.P. Bienert, M.D. Schüssler, T.P. Jahn, Metalloids: essential, beneficial or toxic? Major intrinsic proteins sort it out, Trends Biochem. Sci. 33 (2007) 20–26.
[40] J.A. Raven, Short- and long-distance transport of boric acid in plants, New Phytol. 84 (1980) 231–249.
[41] C. Dordas, P.H. Brown, Permeability of boric acid across lipid bilayers and factors affecting it, J. Membr. Biol. 175 (2000) 95–105.
[42] F. Dannel, H. Pfeffer, V. Römheld, Characterization of root boron pools, boron uptake and boron translocation in sunflower using the stabile isotopes 10B and 11B, Austr. J. Plant Physiol. 27 (2000) 397–405.
[43] J.C.R. Stangoulis, R.J. Reid, P.H. Brown, R.D. Graham, Kinetic analysis of boron transport in Chara, Planta 213 (2001) 142–146.
[44] C. Dordas, P.H. Brown, Evidence for channel mediated transport of boric acid in squash (Cucurbita pepo), Plant Soil 235 (2001) 95–103.

[45] C. Dordas, M.J. Chrispeels, P.H. Brown, Permeability and channel-mediated transport of boric acid across membrane vesicles isolated from squash roots, Plant Physiol. 124 (2000) 1349–1361.
[46] J. Takano, K. Noguchi, M. Yasumori, M. Kobayashi, Z. Gajdos, K. Miwa, H. Hayashi, T. Yoneyama, T. Fujiwara, Arabidopsis boron transporter for xylem loading, Nature 420 (2002) 337–340.
[47] J. Takano, M. Wada, U. Ludewig, G. Schaaf, N. von Wirén, T. Fujiwara, The arabidopsis major intrinsic protein NIP5;1 is essential for efficient boron uptake and plant development under boron limitation, Plant Cell 18 (2006) 1498–1509.
[48] M. Tanaka, I.S. Wallace, J. Takano, D.M. Roberts, T. Fujiwara, NIP6;1 is a boric acid channel for preferential transport of boron to growing shoot tissues in arabidopsis, Trans. Faraday Soc. 20 (2008) 2860–2875.
[49] J.E. Hayes, R.J. Reid, Boron tolerance in barley is mediated by efflux of boron from the roots, Plant Physiol. 136 (2004) 3376–3382.
[50] Y. Del-Amo, M.A. Brzezinski, The chemical form of dissolved Si taken up by marine diatoms, J. Phycol. 35 (1999) 1162–1170.
[51] Y. Chiba, N. Mitani, N. Yamaji, J.F. Ma, HvLsi1 is a silicon influx transporter in barley, Plant J. 57 (2009) 810–818.
[52] G.P. Bienert, M. Thorsen, M.D. Schüssler, H.R. Nilsson, A. Wagner, M.J. Tamás, T.P. Jahn, A subgroup of plant aquaporins facilitate the bi-directional diffusion of $As(OH)_3$ and $Sb(OH)_3$ across membranes, BMC Biol. 6 (2008) 26.
[53] J.F. Ma, N. Yamaji, N. Mitani, K. Tamai, S. Konishi, T. Fujiwara, M. Katsuhara, M. Yano, An efflux transporter of silicon in rice, Nature 448 (2007) 209–212.
[54] M. Hildebrand, B.E. Volcani, W. Gassmann, J.I. Schroeder, A gene family of silicon transporters, Nature 385 (1997) 688–689.
[55] K. Thamatrakoln, M. Hildebrand, Analysis of thalassiosira pseudonana silicon transporters indicates distinct regulatory levels and transport activity through the cell cycle, Eukaryot. Cell 6 (2007) 271–279.
[56] R.-N. Huang, T.-C. Lee, Cellular uptake of trivalent arsenite and pentavalent arsenate in KB cells cultured in phosphate-free medium, Toxicol. Appl. Pharmacol. 136 (1996) 243–249.
[57] H. Rosenberg, R.G. Gerdes, K. Chegwidden, Two systems for the uptake of phosphate in *Escherichia coli*, J. Bacteriol. 131 (1977) 505–511.
[58] L.V. Virkki, J. Biber, H. Murer, I.C. Forster, Phosphate transporters: a tale of two solute carrier families, Am. J. Physiol. Renal Physiol. 293 (2007) F643–F654.
[59] B.L. Persson, J. Petersson, U. Fristedt, R. Weinander, A. Berhe, J. Pattison, Phosphate permeases of *Saccharomyces cerevisiae*: structure, function and regulation, Biochim. Biophys. Acta 1422 (1999) 255–272.
[60] R. Wysocki, M.J. Tamás, How *Saccharomyces cerevisiae* copes with toxic metals and metalloids, FEMS Microbiol. Rev. 34 (2010) 925–951.
[61] G.P. Bienert, T.P. Jahn, Major intrinsic proteins and arsenic transport in plants: new players and their potential role, in: T.P. Jahn, G.P. Bienert (Eds.), MIPs and Their Roles in the Exchange of Metalloids, vol. 679 of Advances in Experimental Medicine and Biology, Landes Bioscience, 2010, pp. 111–125.
[62] R. Mukhopadhyay, D. Bisacchi, Y. Zhou, A. Armirotti, D. Bordo, Structural characterization of the As/Sb reductase LmACR2 from Leishmania major, J. Mol. Biol. 386 (2009) 1229–1239.
[63] G. Ji, S. Silver, Reduction of arsenate to arsenite by the ArsC protein of the arsenic resistance operon of Staphylococcus aureus plasmid pI258, Proc. Natl. Acad. Sci. USA 89 (1992) 9474–9478.
[64] P. Bobrowicz, R. Wysocki, G. Owsianik, A. Goffeau, S. Ułaszewski, Isolation of three contiguous genes, *ACR1*, *ACR2* and *ACR3*, involved in resistance to arsenic compounds in the yeast *Saccharomyces cerevisiae*, Yeast 13 (1997) 819–828.
[65] R. Mukhopadhyay, J. Shi, B.P. Rosen, Purification and characterization of Acr2p, the *Saccharomyces cerevisiae* arsenate reductase, J. Biol. Chem. 275 (2000) 21149–21157.
[66] C.-M. Chen, T.K. Misra, S. Silver, B.P. Rosen, Nucleotide sequence of the structural genes for an anion pump, J. Biol. Chem. 261 (1986) 15030–15038.
[67] I. Zegers, J.C. Martins, R. Willem, L. Wyns, J. Messens, Arsenate reductase from *S. aureus* plasmid pI258 is a phosphatase drafted for redox duty, Nature Struct. Biol. 8 (2001) 843–847.
[68] P. Martin, S. DeMel, J. Shi, D.L. Gatti, B.P. Rosen, B.F.P. Edwards, Insights into the structure, solvation, and mechanism of ArsC arsenate reductase, a novel arsenic detoxification enzyme, Structure 9 (2001) 1071–1081.
[69] T. Krafft, J.M. Macy, Purification and characterization of the respiratory arsenate reductase of Chrysiogenes arsenatis, Eur. J. Biochem. 255 (1998) 647–653.
[70] T.R. Radabaugh, H.V. Aposhian, Enzymatic reduction of arsenic compounds in mammalian systems: reduction of arsenate to arsenite by human liver arsenate reductase, Chem. Res. Toxicol. 13 (2000) 26–30.
[71] B.P. Rosen, Biochemistry of arsenic detoxification, FEBS Lett. 529 (2002) 86–92.
[72] Y. Zhou, N. Messier, M. Ouellette, B.P. Rosen, R. Mukhopadhyay, Leishmania major LmACR2 is a pentavalent antimony reductase that confers sensitivity to the drug pentostam, J. Biol. Chem. 279 (2004) 37445–37451.
[73] Y. Zhou, H. Bhattacharjee, R. Mukhopadhyay, Bifunctional role of the leishmanial antimonate reductase LmACR2 as a protein tyrosine phosphatase, Mol. Biochem. Parasit. 148 (2006) 161–168.
[74] C. dos Santos Ferreira, P.S. Martins, C. Demicheli, C. Brochu, M. Ouellette, F. Frézard, Thiol-induced reduction of antimony(V) into antimony(III): a comparative study with trypanothione, cysteinyl-glycine, cysteine and glutathione, BioMetals 16 (2003) 441–446.
[75] P. Shaked-Mishan, N. Ulrich, M. Ephros, D. Zilberstein, Novel intracellular Sb^V reducing activity correlates with antimony susceptibility in *Leishmania donovani*, J. Biol. Chem. 276 (2001) 3971–3976.
[76] H. Denton, J.C. McGregor, G.H. Coombs, Reduction of anti-leishmanial pentavalent antimonial drugs by a parasite-specific thiol-dependent reductase, TDR1, Biochem. J. 381 (2004) 405–412.
[77] H. Bhattacharjee, R. Mukhopadhyay, S. Thiyagarajan, B.P. Rosen, Aquaglyceroporins: ancient channels for metalloids, J. Biol. 7 (2008) 33.
[78] R. Wysocki, C.C. Chéry, D. Wawrzycka, M.V. Hulle, R. Cornelis, J.M. Thevelein, M.J. Tamás, The glycerol channel Fps1p mediates the uptake of arsenite and antimonite in *Saccharomyces cerevisiae*, Mol. Microbiol. 40 (2001) 1391–1401.
[79] O.I. Sanders, C. Rensing, M. Kuroda, B. Mitra, B.P. Rosen, Antimonite is accumulated by the glycerol facilitator GlpF in *Escherichia coli*, J. Bacteriol. 179 (1997) 3365–3367.
[80] Y.-L. Meng, Z. Liu, B.P. Rosen, As(III) and Sb(III) uptake by GlpF and efflux by ArsB in *Escherichia coli*, J. Biol. Chem. 279 (2004) 18334–18341.
[81] F.J.M. Stanislav, V. Isayenkov, The Arabidopsis thaliana aquaglyceroporin AtNIP7;1 is a pathway for arsenite uptake, FEBS Lett. 582 (2008) 1625–1628.
[82] Z. Liu, J. Shen, J.M. Carbrey, R. Mukhopadhyay, P. Agre, B.P. Rosen, Arsenite transport by mammalian aquaglyceroporins AQP7 and AQP9, Proc. Natl. Acad. Sci. USA 99 (2002) 6053–6058.
[83] H. Bhattacharjee, J. Carbrey, B.P. Rosen, R. Mukhopadhyay, Drug uptake and pharmacological modulation of drug sensitivity in leukemia by AQP9, Proc. Natl. Acad. Sci. USA 322 (2004) 836–841.
[84] J. Leung, A. Pang, W.-H. Yuen, Y.-L. Kwong, E.W.C. Tse, Relationship of expression of aquaglyceroporin 9 with arsenic uptake and sensitivity in leukemia cells, Blood 109 (2007) 740–746.
[85] Y. Shinkai, D. Sumi, T. Toyama, T. Kaji, Y. Kumagai, Role of aquaporin 9 in cellular accumulation of arsenic and its cytotoxicity in primary mouse hepatocytes, Toxicol. Appl. Pharm. 237 (2009) 232–236.
[86] B. Gourbal, N. Sonuc, H. Bhattacharjee, D. Legare, S. Sundar, M. Ouellette, B.P. Rosen, R. Mukhopadhyay, Drug uptake and modulation of drug resistance in *Leishmania* by an Aquaglyceroporin, J. Biol. Chem. 279 (2004) 31010–31017.
[87] N. Marquis, B. Gourbal, B.P. Rosen, R. Mukhopadhyay, M. Ouellette, Modulation in aquaglyceroporin AQP1 gene transcript levels in drug-resistant *Leishmania*, Mol. Microbiol. 57 (2005) 1690–1699.
[88] K. Figarella, N.L. Uzcategui, Y. Zhou, A. LeFurgey, M. Ouellette, H. Bhattacharjee, R. Mukhopadhyay, Biochemical characterization of *Leishmania* major aquaglyceroporin LmAQP1: possible role in volume regulation and osmotaxis, Mol. Microbiol. 65 (2007) 1006–1017.
[89] Z. Liu, J.M. Carbrey, P. Agre, B.P. Rosen, Arsenic trioxide uptake by human and rat aquaglyceroporins, Biochem. Biophys. Res. Commun. 316 (2004) 1178–1185.
[90] H.-C. Yang, J. Cheng, T.M. Finan, B.P. Rosen, H. Bhattacharjee, Novel pathway for arsenic detoxification in the legume symbiont sinorhizobium meliloti, J. Bacteriol. 187 (2005) 6991–6997.
[91] J.F. Ma, N. Yamaji, N. Mitani, X.-Y. Xu, Y.-H. Su, S.P. McGrath, F.-J. Zhao, Transporters of arsenite in rice and their role in arsenic accumulation in rice grain, Proc. Natl. Acad. Sci. USA 105 (2008) 9931–9935.
[92] Z. Liu, M.A. Sanchez, X. Jiang, E. Boles, S.M. Landfear, B.P. Rosen, Mammalian glucose permease GLUT1 facilitates transport of arsenic trioxide and methylarsonous acid, Biochem. Biophys. Res. Commun. 351 (2006) 424–430.
[93] R. Wysocki, P. Bobrowicz, S. Ułaszewski, The *Saccharomyces cerevisiae* ACR3 gene encodes a putative membrane protein involved in arsenite transport, Proc. Natl. Acad. Sci. USA 48 (1997) 30061–30066.
[94] M. Ghosh, J. Shen, B.P. Rosen, Pathways of As(III) detoxification in *Saccharomyces cerevisiae*, Proc. Natl. Acad. Sci. USA 96 (1999) 5001–5006.
[95] E. Maciaszczyk-Dziubinskaa, M. Migockaa, R. Wysocki, Acr3p is a plasma membrane antiporter that catalyzes $As(III)/H^+$ and $Sb(III)/H^+$ exchange in *Saccharomyces cerevisiae*, Biochim. Biophys. Acta 1808 (2011) 1855–1859.
[96] H.L. Mobley, B.P. Rosen, Energetics of plasmid-mediated arsenate resistance in *Escherichia coli*, Proc. Natl. Acad. Sci. USA 79 (1982) 6119–6122.
[97] S. Dey, D. Dou, B.P. Rosen, ATP-dependent arsenite transport in everted membrane vesicles of *Escherichia coli*, J. Biol. Chem. 269 (1994) 25442–25446.
[98] M.J. Tamás, R. Wysocki, Mechanisms involved in metalloid transport and tolerance acquisition, Curr. Genet. 40 (2001) 2–12.
[99] S.V. Kala, M.W. Neely, G. Kala, C.I. Prater, D.W. Atwood, J.S. Rice, M.W. Lieberman, The MRP2/cMOAT transporter and arsenic-glutathione complex formation are required for biliary excretion of arsenic, J. Biol. Chem. 275 (2000) 33404–33408.
[100] D. Légaré, D. Richard, R. Mukhopadhyay, Y.-D. Stierhof, B.P. Rosen, A. Haimeur, B. Papadopoulou, M. Ouellette, The *Leishmania* ATP-binding cassette protein PGPA is an intracellular metal-thiol transporter ATPase, J. Biol. Chem. 276 (2001) 26301–26307.
[101] R.G. Deeley, S.P.C. Cole, Function, evolution and structure of multidrug resistance protein (MRP), Semin. Cancer Biol. 8 (1997) 193–204.
[102] M. Ouellette, A. Haimeur, K. Grondin, D. Légaré, B. Papadopoulou, Amplification of ABC transporter gene pgpA and of other heavy metal resistance genes in *Leishmania* tarentolae and their study by gene transfection and gene disruption, Method Enzymol. 292 (1998) 182–193.
[103] S.P. Cole, G. Bhardwaj, J.H. Gerlach, J.E.M.C.E. Grant, K.C. Almquist, A.J. Stewart, E.U. Kurz, A.M. Duncan, R.G. Deeley, Overexpression of a transporter gene in a multidrug-resistant human lung cancer cell line, Science 258 (1992) 1650–1654.

[104] S.P. Cole, K.E. Sparks, K. Fraser, D.W. Loe, C.E. Grant, G.M. Wilson, R.G. Deeley, Pharmacological characterization of multidrug resistant MRP-transfected human tumor cells, Cancer Res. 54 (1994) 5902–5910.
[105] G.J. Zaman, J.L.O. van Tellingen, J. Beijnen, H. Dekker, C. Paulusma, R.P.O. Elferink, F. Baas, P. Borst, Role of glutathione in the export of compounds from cells by the multidrug-resistance-associated protein, Proc. Natl. Acad. Sci. USA 92 (1995) 7690–7694.
[106] L. Vernhet, A. Courtois, N. Allain, L. Payen, J.-P. Anger, A. Guillouzo, O. Fardel, Overexpression of the multidrug resistance-associated protein (MRP1) in human heavy metal-selected tumor cells, FEBS Lett. 443 (1999) 321–325.
[107] A. Haimeur, C. Brochu, P.-A. Genest, B. Papadopoulou, M. Ouellette, Amplification of the ABC transporter gene PGPA and increased trypanothione levels in potassium antimonyl tartrate (SbIII) resistant Leishmania tarentolae, Mol. Biochem. Parasitol. 108 (2000) 131–135.
[108] C.S. Cobbett, Phytochelatins and their roles in heavy metal detoxification, Plant Physiol. 123 (2000) 825–832.
[109] O.K. Vatamaniuk, E.A. Bucher, J.T. Ward, P.A. Rea, Worms take the 'phyto' out of 'phytochelatins', Trends Biotechnol. 20 (2002) 61–64.
[110] M.E. Schmöger, M. Oven, E. Grill, Detoxification of arsenic by phytochelatins in plants, Plant Physiol. 122 (2000) 793–801.
[111] J. Hartley-Whitaker, G. Ainsworth, R. Vooijs, W.T. Bookum, H. Schat, A.A. Meharg, Phytochelatins are involved in differential arsenate tolerance in *Holcus lanatus*, Plant Physiol. 126 (2001) 299–306.
[112] F. Challenger, Biological methylation, Chem. Rev. 36 (1945) 315–361.
[113] M. Filella, N. Belzile, M.-C. Lett, Antimony in the environment: a review focused on natural waters: III. Microbiota relevant interactions, Earth-Sci. Rev. 80 (2007) 195–217.
[114] R.O. Jenkins, Microbial biomethylation of antimony, Trends Organomet. Chem. 4 (2002) 109–122.
[115] R.O. Jenkins, A.W. Ritchie, J.S. Edmonds, W. Goessler, N. Molenat, D. Kuehnelt, C.F. Harrington, P.G. Sutton, Bacterial degradation of arsenobetaine via dimethylarsinoylacetate, Arch. Microbiol. 180 (2003) 142–150.
[116] L. Duester, R.A. Diaz-Bone, J. Kösters, A.V. Hirner, Methylated arsenic, antimony and tin species in soils, J. Environ. Monit. 7 (2005) 1186–1193.
[117] Z. Liu, M. Styblo, B.P. Rosen, Methylarsonous acid transport by Aquaglyceroporins, Environ. Health Persp. 114 (2006) 527–531.
[118] X.-Y. Meng, J. Qin, L.-H. Wang, G.-L. Duan, G.-X. Sun, H.-L. Wu, C.-C. Chu, H.-Q. Ling, B.P. Rosen, Y.-G. Zhu, Arsenic biotransformation and volatilization in transgenic rice, New Phytol. 191 (2011) 49–56.
[119] R.-Y. Li, Y. Ago, W.-J. Liu, N. Mitani, J. Feldmann, S.P. McGrath, J.F. Ma, F.-J. Zhao, The rice Aquaporin Lsi1 mediates uptake of methylated arsenic species, Plant Physiol. 150 (2009) 2071–2080.
[120] D. Napierska, L.C.J. Thomassen, D. Lison, J.A. Martens, P.H. Hoet, The nanosilica hazard: another variable entity, Part. Fibre Toxicol. 7 (2010) 39.
[121] T.K. Barik, B. Sahu, V. Swain, Nanosilica-from medicine to pest control, Parasitol. Res. 103 (2008) 253–258.
[122] M. Chen, A. von Mikecz, Formation of nucleoplasmic protein aggregates impairs nuclear function in response to SiO_2 nanoparticles, Exp. Cell. Res. 305 (2005) 51–62.
[123] T.-G. Iversen, T. Skotland, K. Sandvig, Endocytosis and intracellular transport of nanoparticles: present knowledge and need for future studies, Nano Today 6 (2011) 176–185.
[124] F. Lu, S.-H. Wu, Y. Hung, C.-Y. Mou, Size effect on cell uptake in well-suspended, uniform mesoporous silica nanoparticles, Small 5 (2009) 1408–1413.
[125] L. Hu, Z. Mao, Y. Zhang, C. Gao, Influences of size of silica particles on the cellular endocytosis, exocytosis and cell activity of HepG2 cells, J. Nanosci. Lett. 1 (2011) 1–16.
[126] D.-M. Huang, Y. Hung, B.-S. Ko, S.-C. Hsu, W.-H. Chen, C.-L. Chien, C.-P. Tsai, C.-T. Kuo, J.-C. Kang, C.-S. Yang, C.-Y. Mou, Y.-C. Chen, Highly efficient cellular labeling of mesoporous nanoparticles in human mesenchymal stem cells: implication for stem cell tracking, FASEB J. 19 (2005) 2014–2016.
[127] I. Slowing, B.G. Trewyn, V.S.-Y. Lin, Effect of surface functionalization of MCM-41-type mesoporous silica nanoparticles on the endocytosis by human cancer cells, J. Am. Chem. Soc. 128 (2006) 14792–14793.
[128] T.-H. Chung, S.-H. Wu, M. Yao, C.-W. Lu, Y.-S. Lin, Y. Hung, C.-Y. Mou, Y.-C. Chen, D.-M. Huang, The effect of surface charge on the uptake and biological function of mesoporous silica nanoparticles in 3T3-L1 cells and human mesenchymal stem cells, Biomaterials 28 (2007) 2959–2966.
[129] C.-W. Lu, Y. Hung, J.-K. Hsiao, M. Yao, T.-H. Chung, Y.-S. Lin, S.-H. Wu, S.-C. Hsu, H.-M. Liu, C.-Y. Mou, C.-S. Yang, D.-M. Huang, Y.-C. Chen, Bifunctional magnetic silica nanoparticles for highly efficient human stem cell labeling, Nano Lett. 7 (2007) 149–154.
[130] G. Orr, D.J. Panther, J.L. Phillips, B.J. Tarasevich, A. Dohnalkova, D. Hu, J.G. Teeguarden, J.G. Pounds, Submicrometer and nanoscale inorganic particles exploit the actin machinery to be propelled along microvilli-like structures into alveolar cells, ACS Nano 1 (2007) 463–475.
[131] Q. He, Z. Zhang, Y. Gao, J. Shi, Y. Li, Intracellular localization and cytotoxicity of spherical mesoporous silica nano- and microparticles, Small 5 (2009) 2722–2729.
[132] J.-K. Hsiao, C.-P. Tsai, T.-H. Chung, Y. Hung, M. Yao, H.-M. Liu, C.-Y. Mou, C.-S. Yang, Y.-C. Chen, D.-M. Huang, Mesoporous silica nanoparticles as a delivery system of gadolinium for effective human stem cell tracking, Small 4 (2008) 1445–1452.
[133] G. Orr, D.J. Panther, K.J. Cassens, J.L. Phillips, B.J. Tarasevich, J.G. Pounds, Syndecan-1 mediates the coupling of positively charged submicrometer amorphous silica particles with actin filaments across the alveolar epithelial cell membrane, Toxicol. Appl. Pharmacol. 5 (2009) 296–311.
[134] E. Witasp, N. Kupferschmidt, L. Bengtsson, K. Hultenby, C. Smedman, S. Paulie, A.E. Garcia-Bennett, B. Fadeel, Efficient internalization of mesoporous silica particles of different sizes by primary human macrophages without impairment of macrophage clearance of apoptotic or antibody-opsonized target cells, Toxicol. Appl. Pharmacol. 239 (2009) 306–319.
[135] J. Choi, Q. Zheng, H.E. Katz, T.R. Guilarte, Silica-based nanoparticle uptake and cellular response by primary microglia, Environ. Health Perspect. 118 (2010) 589–595.
[136] E.B. Gyenge, X. Darphin, A. Wirth, U. Pieles, H. Walt, M. Bredell, C. Maake, Uptake and fate of surface modified silica nanoparticles in head and neck squamous cell carcinoma, J. Nanobiotechnol. 9 (2011) 32.
[137] H. Nabeshi, T. Yoshikawa, K. Matsuyama, Y. Nakazato, S. Tochigi, S. Kondoh, T. Hirai, T. Akase, K. Nagano, Y. Abe, Y. Yoshioka, H. Kamada, N. Itoh, S.i. Tsunoda, Y. Tsutsumi, Amorphous nanosilica induce endocytosis-dependent ROS generation and DNA damage in human keratinocytes, Part. Fibre Toxicol. 8 (2011) 1.
[138] G.A. Orr, W.B. Chrisler, K.J. Cassens, R. Tan, B.J. Tarasevich, L.M. Markillie, R.C. Zangar, B.D. Thrall, Cellular recognition and trafficking of amorphous silica nanoparticles by macrophage scavenger receptor A, Nanotoxicology 5 (2011) 296–311.