Thiolated arsenic in natural systems: What is current, what is new and what needs to be known

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ABSTRACT

Thiolated arsenic compounds are the sulfur analogous substructures of oxo-arsenicals as the arsinoyl (As = O) is substituted by an arsinothioyl (As = S) group. Relatively brief history of thioarsenic research, mostly in the current decade has endeavored to understand their consequences in the natural environment. However, thioarsenic related aspects have by far not attached much research concern on global scale compared to other arsenic species. This review attempts to provide a critical overview for the first time on formation mechanisms of thioarsenicals, their chemistry, speciation and analytical methodologies in order to provide a rational assessment of what is new, what is current, what needs to be known or what should be done in future research. Thioarsenic compounds play a vital role in determining the biogeochemistry of arsenic in sulfidic environments under reducing conditions. Thioarsenic species are widely immobilized by naturally occurring processes such as the adsorption on iron (oxyhydr)oxides and precipitation on iron sulfide minerals. Accurate measurement of thioarsenic species is a challenging task due to their instability upon pH, temperature, redox potential, and concentrations of oxygen, sulfur and iron. Assessment of direct and indirect effects of toxic thioarsenic species on global population those who frequently get exposed to high levels of arsenic is an urgent necessity. Dimethylmonothioarsinic acid ($DMMTA^{V}$) is the most cytotoxic arsenic metabolite having similar toxicological effects as dimethylarsinous acid (DMA^{III}) in human and animal tissues. The formation and chemical analysis of thioarsenicals in soil and sediments are highly unknown. Therefore, future research needs to be more inclined towards in determining the molecular structure of unknown thioarsenic complexes in various environmental suites. Contemporary approaches hyphenated to existing technologies would pave the way to overcome critical challenges of thioarsenic speciation such as standards synthesis, structural determination, quantification and sample preservation in future research.

1. Introduction

Arsenic (As) and sulfur (S) commonly co-exist in the environment due to their strong interrelationship in the biogeochemical cycles (Härtig and Planer-Friedrich, 2012). Arsenic species where the oxygen-bonded As is substituted by sulfur, thereby forming As-SH and/or As = S substructures are known as thioarsenic compounds which can increase the complexity of As species and related geochemical, environmental and biological processes (Maher et al., 2013). Geothermal systems, marine and lacustrine sediments contain high concentrations of sulfide (S^{2-}/HS^{-}), where thioarsenicals may constitute a significant fraction (up to 80%) of the total levels of As. Occurrence of thioarsenic species has been identified as a vital parameter to better understand the geologic and geochemical mechanisms of As enrichment in sulfide rich waters (Guo et al., 2017). Therefore, an inclusive understanding of the formation, speciation and chemical analysis of thioarsenic species is crucial for investigating the fate of As in different environmental, geological, and biological systems.

Thioarsenic compounds can occur in sulfidic waters as either thioarsenates (As(V)-S species) or thioarsenites (As(III)-S species) and

the dissolved species of such thioarsenicals play a vital role in determining the biogeochemistry of As in sulfidic environments under reducing conditions (Planer-Friedrich et al., 2017). It has been reported that thioarsenates can occur in groundwater, slags, geothermal fluids, wetland porewater, and flooded rice paddy soil (Härtig and Planer-Friedrich, 2012; Planer-Friedrich and Wilson, 2012; Price et al., 2010; Price et al., 2009; Suess et al., 2011; Ullrich et al., 2016). For instance, thioarsenate is detected in geothermal waters up to 80% of the total As concentrations (Planer-Friedrich et al., 2007; Ullrich et al., 2013), whereas it decreases up to 50% in wetland porewater due to the presence of ferrous ion (Suess et al., 2015; Suess et al., 2011). Interestingly, thioarsenates tend to be immobilized by some naturally occurring processes such as the adsorption on iron (oxyhydr)oxides and precipitation on iron sulfide minerals. However, the immobilization of thioarsenates by aforementioned naturally occurring mineral phases is lower than that of arsenite and arsenate species and hence, the serious consequences of thioarsenates are of particular concern in terms of their high mobility and bioavailability in the natural environment.

Although As is well known to be the one of emerging carcinogenic metalloids, toxicological effects of thioarsenicals are not adequately studied in nature. It has been reported that the microbiota living in human and animal gut can enhance the production of inorganic as well as methylated thioarsenate compounds due to complexation reactions between thiol groups and ingested arsenates in the gut (Van de Wiele et al., 2010). The replacement of OH^- groups of methylated arsenic species by SH^- (thiolation) can occur in H_2S producing gut microbiota within the distal gastrointestinal tract (Hinrichsen et al., 2015). For instance, highly toxic dimethylmonothioarsenate (LC_{50} - 10.7 in cultured A431 human epidermoid carcinoma cells) is formed by the thiolation of dimethylarsenate during the metabolism of dimethylarsenate in human urine (Kim et al., 2016). It has been found that the toxicity of thioarsenates is 10- and 100-fold higher than that of methylarsenates for hepatocyte and urothelial cells, respectively (Leffers et al., 2013; Naranmandura et al., 2011). In terms of the implications of thioarsenic species on plants, the uptake, accumulation, toxicity and tolerance of monothioarsenate have been successfully studied in *Arabidopsis thaliana* plants (Planer-Friedrich et al., 2017). However, little is known regarding hazardous consequences of thioarsenic complexes on human health as well as agricultural crop productivity.

A critical review of biological consequences of thioarsenicals on As metabolism, toxicity, and therapeutic effects was recently presented (Sun et al., 2016). Another attempt has been made to quantify the thioarsenic species in marine macroalgae and herbivorous animals that are found along the south east coast line in Australian (Foster and Maher, 2016). Moreover, the formation of thiol complexes with accumulated inorganic and organic arsenic in rice plant tissues has been reported in a very recent study (Mishra et al., 2017; Planer-Friedrich et al., 2017). However, the definite chemical nature of most of thioarsenic compounds still remains a subject of debate and hence, it is urgently necessary to develop proper analytical protocols for resolving this dispute in order to understand mechanisms of As speciation, geochemistry, and mobility in sulfur rich environments. Therefore, the present review attempts to provide a critical integrated overview of what is new, what is current, what needs to be known or what should be done in future research on the interdisciplinary topics of the formation mechanisms of thiolated As complexes, their chemistry, toxicity and analytical methodologies. Overall, this critical review provides a comprehensive discussion for the first time on (i) formation mechanisms of thioarsenic complexes and their chemistry (ii) occurrence, (iii) speciation and (iv) chemical analysis in order to identify the future research needs on thioarsenic related aspects in a variety of environmental suites.

2. Formation of thioarsenicals

Thioarsenic compounds are formed as a result of geochemical interactions between As and sulfur-containing compounds (sulfides; S^{2-}/HS^-) in favourably reducing or anoxic environments (Wallschläger and Stadey, 2007; Webster, 1990). The formation of thioarsenic compounds from arsenite in sulfidic environments was investigated by using solubility studies under laboratory conditions in the 19th century (Brauner and Tomícek, 1887; Planer-Friedrich and Scheinost, 2011). Moreover, laboratory and field scale studies have demonstrated the formation pathways of thioarsenic complexes in sulfidic water containing both inorganic arsenates and arsenites (Beak et al., 2008; Bostick et al., 2005; Hollibaugh et al., 2005; Wilkin et al., 2003; Wood et al., 2002; Wu et al., 2017). It has been investigated that thioarsenic compounds are formed in natural systems through oxidation of arsenite [As(III)] in sulfidic environments and dissolution of arsenic sulfide minerals.

2.1. Formation of thioarsenic complexes by sulfur-arsenite/arsenate interactions

Thioarsenic complexes in the form of thioarsenates are formed through a series of redox reactions between As(III) and sulfur while donating non-bonding electron pair of arsenite to sulfur atom. The formation of thioarsenates takes place through the deprotonation of arsenite in the presence of aqueous sulfide (H_2S), where arsenite is partially oxidized to monothioarsenate while sulfide is getting reduced (reaction 1) (Burton et al., 2013; Stauder et al., 2005). It has been examined under laboratory conditions that this reaction is feasible at the concentration of H_3AsO_3; 91 μM, ratio H_2S/HS^-; 5000 μM and neutral pH (~7 pH) (Stauder et al., 2005). In natural environments, including some ground and geothermal fluids, this reaction occurs due to presence of electron acceptors such as sulfate and sulfur which are produced from H_2S by bacterial activities:

$$5H_3AsO_{3(aq)} + 3H_2S_{(aq)} \rightarrow 2As_{(s)} + 3H_2AsO_3S^-_{(aq)} + 6H_2O_{(l)} + 3H^+_{(aq)} \quad (1)$$

The monothioarsenate produced from reaction (1) is further converted to dithioarsenate in the presence of excess sulfide (reaction 2).

$$H_2AsO_3S^-_{(aq)} + H_2S_{(aq)} \rightarrow H_2AsO_2S^-_{2(aq)} + H_2O_{(l)} \quad (2)$$

On the other hand, it has been revealed a potential pathway to produce thioarsenites in an aqueous solution of arsenite and excess sulfide under reducing conditions as expressed by reaction 3 (Price et al., 2010). In this reaction pathway, trithioarsenite is produced as the primary reaction product and subsequently the trithioarsenite is willingly oxidized to di-, and tri-thioarsenate under oxic conditions (reactions 4 and 5). These reactions can possibly occur in some aquifers associated with sulfidic geothermal reservoirs where uprising geothermal water mixes with aerobic groundwater.

$$H_3AsO_{3(aq)} + 3H_2S_{(aq)} \rightarrow H_3AsS_{3(aq)} + 3H_2O_{(l)} \quad (3)$$

$$H_3AsS_{3(aq)} + O_{2(g)} \rightarrow H_3AsO_2S_{2(aq)} + S_{(s)} \quad (4)$$

$$2H_3AsS_{3(aq)} + 2O_{2(g)} \rightarrow 2H_3AsOS_{3(aq)} + O_{2(aq)} \quad (5)$$

The process by which the oxidation of arsenite by elemental sulfur (S°) is known as the third potential pathway for the formation of thioarsenates (reaction 6).

$$H_3AsO_{3(aq)} + S_{(s)} \rightarrow H_2AsO_3S^-_{(aq)} + H^+_{(aq)} \quad (6)$$

In natural environments, the elemental sulfur tends to be produced as a result of interactions between iron (oxyhydr)oxides (goethite) and dissolved H_2S as expressed by reaction 7 (Poulton et al., 2004).

$$2Fe(OH)_3 + H_2S_{(aq)} + 4H^+_{(aq)} \rightleftharpoons 2Fe^{2+}_{(aq)} + S_{(s)} + 6H_2O_{(l)} \quad (7)$$

One of very recent studies revealed that microbial activities of sulfate-reducing bacteria, such as *Desulfotomaculum* can strongly influence the formation of thioarsenate from the oxidation of arsenite in sulfidic geothermal water (Wu et al., 2017). In sulfidic aquifers under anoxic

conditions, *Desulfotomaculum* bacterium can oxidize arsenite to arsenate which can react with S^{2-}/HS^{-}, thereby producing thioarsenates ($AsO_{4-x}S_x^{2-}$ with x = 1–4) along with mono-, di-, and tri-thioarsenate as dominant species (reaction 8) (Wu et al., 2017).

$$[HAs(V)O_4]^{2-} + [HS]^{-} \rightarrow [HAs(V)S^{2-}xO_{4-x}]^{2-} + [OH]^{-}$$
$$x = 1 - 4 \quad (8)$$

Reactions of arsenates in sulfidic water can be predominately used to determine the equilibrium of As speciation in the presence of excess sulfide. Based on laboratory experiments, previous studies have demonstrated that these arsenate reduction reactions (reactions 9 and 10) can take place in the presence of 3–4-fold excess of sulfide levels compared to the concentration of arsenates (Burton et al., 2013). However, the rate of arsenate reduction by aqueous sulfide is extremely pH dependent and these reductions are very rapid under acidic conditions. It has experimentally proven that the arsenate reduction process is not feasible at near-neutral pH with even 100-time excess concentrations of sulfide (sulfide: arsenate = 100: 1) (Rochette et al., 2000). This study found that arsenate reduction by H_2S is followed by the second-order kinetics giving a rate constant (k) of $3.2 \times 10^2\ M^{-1}\ h^{-1}$ at pH 4 which is almost 300 times greater than the reduction rate of arsenate at pH 7.

$$AsO_{4(aq)}^{3-} + 4H_2S_{(aq)} \rightarrow AsS_{4(aq)}^{3-} + 4H_2O_{(l)}$$
$$\log k = 61.9 \quad (9)$$

$$AsO_{4(aq)}^{3-} + 3H_2S_{(aq)} + H_{(aq)}^{+} \rightarrow HAsS_3O_{(aq)}^{2-} + 3H_2O_{(l)}$$
$$\log k = 56.9 \quad (10)$$

2.2. Formation of thioarsenicals by dissolution of arsenic sulfide minerals

Arsenic bearing sulfide minerals, specifically orpiment (As_2S_3), enargite (Cu_3AsS_4) and arsenopyrite (As-Fe-S) are important sources of the formation of various thioarsenic species in the environment (Suess and Planer-Friedrich, 2012; Tossell, 2001). Dissolution of these mineral phases may trigger the release and formation of thioarsenic compounds which play a crucial role in As cycle in aqueous sulfidic systems. However, important aspects regarding the analytical evidence, dissolution kinetics, redox-potential and oxygen dependency have not been systematically investigated.

2.2.1. Orpiment dissolution

The dissolution of crystalline/amorphous As_2S_3 in sulfidic water has been experimentally determined (Eary, 1992; Helz and Tossell, 2008; Weissberg et al., 1966; Wilkin et al., 2003). The solubility of As_2S_3 in sulfidic water is controlled by several thioarsenite species and each species possesses multiple protonation states at 25 °C and circum-neutral pH (reaction 11–14) (Wilkin et al., 2003).

$$As_2S_{3(s)} + 4H_2O_{(l)} \rightleftharpoons 2As(OH)_2S_{(aq)}^{-} + HS_{(aq)}^{-} + 3H_{(aq)}^{+}$$
$$\log K = -18.9 \quad (11)$$

$$As_2S_{3(s)} + HS_{(aq)}^{-} + 2H_2O_{(l)} \rightleftharpoons 2As(OH)S_{2(aq)}^{2-} + 3H_{(aq)}^{+}$$
$$\log K = -13.8 \quad (12)$$

$$As_2S_{3(s)} + 3HS_{(aq)}^{-} \rightleftharpoons 2AsS_3H_{(aq)}^{2-} + H_{(aq)}^{+}$$
$$\log K = -2.0 \quad (13)$$

$$As_2S_{3(s)} + 5HS_{(aq)}^{-} + 3H_{(aq)}^{+} \rightleftharpoons 2As(SH)_{4(aq)}^{-}$$
$$\log K = 14.1 \quad (14)$$

The dissolution of amorphous As_2S_3 in sulfide deficient and sulfide rich solutions has been investigated at pH 4.4 ± 0.4 and a range of temperature from 25 to 90 °C (Eary, 1992). In sulfide-deficient solutions ($H_2S < 10^{-3}$ M), H_3AsO_3 is the main product of the dissolution of As_2S_3 and the dissolution reaction can be expressed as;

$$12As_2S_{3(s)} + 3H_2O_{(l)} \rightleftharpoons H_3AsO_{3(aq)} + 32H_2S_{(aq)}$$
$$\log K = -22.4 \quad (15)$$

In sulfide rich solutions ($H_2S > 10^{-3.8}$ M), the solubility of As_2S_3 is controlled by the concentration of H_2S and the dissolution As_2S_3 may result $H_2As_3S_6^{-}$ as the dominant species of As (reaction 16). This trimeric thioarsenite is the solubility controlling species of amorphous or crystalline orpiment in sulfur rich solutions.

$$3As_2S_{3(s)} + 3H_2S_{(aq)} \rightleftharpoons 2H_2As_3S_{6(aq)}^{-} + 2H_{(aq)}^{+} \quad (16)$$

Kinetics of As release and formation of thioarsenic species from the oxidative dissolution of As_2S_3 have been investigated at pH 2–12 and 5 mM of S^{-} concentration (Suess and Planer-Friedrich, 2012). In this study, speciation analyses demonstrated that the formation of thioarsenate from As_2S_3 was insignificant (1%) under acidic conditions (pH 2), whereas at pH 7, As_2S_3 can release thioarsenates at 50% of total As concentrations while producing mono-, di-, and tri-thioarsenate at 8, 11 and 31% respectively. This study further investigated the release kinetics of thioarsenates from the dissolution of As_2S_3 at pH 12. With regard to the leaching time, nearly 55% of thioarsenates was formed from the dissolution of As_2S_3 at pH 12 and it was decreased up to 43% after 144 h while remaining mon-, di-, and tri- thioarsenate in the range of 16–22%. Moreover, the findings of this study suggested the possibility of occurring thioarsenites from the dissolution of As_2S_3 as intermediate species since they are essential precursors for the formation of thioarsenates. However, advanced analytical instruments need to be developed in order to prove such suggestions due to high instability of thioarsenites upon oxic conditions which makes their chemical analysis by IC-ICPMS difficult (Price et al., 2010).

2.2.2. Arsenopyrite dissolution

Formation of thioarsenates during dissolution of arsenopyrite was studied based on dissolution kinetic experiments under oxic, sub-oxic and anoxic conditions (Suess and Planer-Friedrich, 2012). The oxidative dissolution of arsenopyrite in alkaline media produces dominantly monothioarsenates at (ΣAs/ΣS) of 0.8–1.3 (reaction 17) (Suess and Planer-Friedrich, 2012).

$$FeAsS_{(s)} + 6OH_{(aq)}^{-} \rightarrow Fe(OH)_{3(aq)} + H_3AsO_3S_{(aq)} + 6e^{-} \quad (17)$$

The formation of monothioarsenate from arsenopyrite dissolution is governed by a mechanism of physisorption of hydroxide under both oxic and anoxic conditions. First, arsenopyrite reacts with dissolved oxygen and subsequently hydroxyl group is adsorbed via a physisorption mechanism (reactions 18–19).

$$FeAsS_{(s)}.\ O_{2(S)} + H_2O_{(l)} + 2e^{-} \rightarrow FeAsS_{(s)} + H_2O_{2(aq)} + OH_{(aq)}^{-} \quad (18)$$

$$FeAsS.\ OH_{(s)}^{-} \rightarrow Fe(OH)AsS_{(s)} + e^{-} \quad (19)$$

$$Fe(OH)AsS_{(s)}^{-} \rightleftharpoons FeAs(OH)S_{(s)} \quad (20)$$

As a result of these electron transfer reactions, a complex of As-OH-S is formed and thereby resulting in a surface complex of monothioarsenate (reactions 21 and 22).

$$[Fe(OH)AsS_{(s)} \rightarrow FeAs(OH)S_{(s)}] + OH_{(aq)}^{-} \rightleftharpoons Fe(OH)_{3(s)} + As(OH)_3S_{(S)} + 5e^{-} \quad (21)$$

$$As(OH)_3S_{(s)} \rightleftharpoons H_3AsO_3S_{(s)} \quad (22)$$

In the presence of hydroxyl ions, this monothioarsenate formed on the surface of arsenopyrite can be released according to reaction 23.

$$H_3AsO_3S_{(s)} + 3OH_{(aq)}^{-} \rightarrow AsO_3S_{(aq)}^{3-} + 3H_2O_{(l)} \quad (23)$$

Moreover, a previous study has proposed specific reaction pathways for the formation of both mono-and di-thioarsenate from arsenite and sulfide in alkaline solutions (reaction 24 and 25) (Zhang, 2004).

$$AsO_{3(aq)}^{3-} + S_{2(aq)}^{2-} \rightarrow AsO_3S_{(aq)}^{3-} + S_{(aq)}^{2-} \quad (24)$$

$$AsO_{3(aq)}^{3-} + S_{2(aq)}^{2-} + H_2O_{(l)} \rightarrow AsO_2S_{2(aq)}^{3-} + 2OH_{(aq)}^{-} \quad (25)$$

At pH 7, thioarsenates were formed from the oxidative dissolution of arsenopyrite which accounted for only 4% of total As concentrations while leaching arsenite and arsenate at 62 and 34%, respectively. However, at pH 12, the formation of thioarsenate amplified up to 43% which entirely constituted the monothioarsenate species. Under suboxic conditions, the concentration of monothioarsenate increased from 5.0 to 180 μM (14 to 18%) within one to two days at pH 12 and 32 to 450 μM (15 to 26%) at pH 13. Whereas the production of dithioarsenate was insignificant at pH 12 and at 13 pH, it varied from 2 to 6% of the total thioarsenates during first 7 days. Furthermore, monothioarsenate levels equilibrated at concentrations of 210 and 640 μM for pH 12 and 13 respectively, during 7 days to 35 days at sub-oxic conditions. The dissolution of arsenopyrite under anoxic conditions was considerably decreased compared to that of oxic conditions and at alkaline pH (12–13 pH), monothioarsenate (43%) was formed under anoxic conditions than under sub-oxic conditions (20%). This study concluded that the formation of thioarsenates through the dissolution of arsenopyrite is insignificant (< 5%) at neutral pH whereas it is significant at alkaline pH (43%, 19% and 43%) for oxic, suboxic, and anoxic conditions, respectively.

3. Sulfur geochemistry and thioarsenic speciation

Biogeochemical cycling of sulfur can have a strong impact on the speciation of thioarsenicals in the natural environment (Couture and Van Cappellen, 2011). Microbial reduction of sulfate (SO_4^{2-}) is capable of governing the formation of different species of As, including thioarsenic complexes in sulfidic environments (Borch et al., 2010). Existence of thioarsenic species may affect the speciation and redox transformation of As in sulfur rich environments and geological systems such as geothermal fluids, deep groundwater, stratified lakes (with anoxic deep layer), organic-matter rich swamps, peat bogs, and mangrove systems (Helz and Tossell, 2008). In sulfidic environments, zero valent sulfur plays a leading role due to its capability of accepting electrons for the oxidation of As(III) to As(V). Previous modeling data suggest that in sulfur rich environments, the oxidation of As(III) can result As(V) (oxy)thioanions that are thermodynamically stable over a wide range of pH, thereby increasing the dissolution of arsenite mineral phases. Therefore, the formation of thioarsenic complexes may lead to an increased solubility and mobility of As species in anoxic environments.

3.1. General speciation of thioarsenic compounds

Thioarsenicals have been identified as an important group of As species and these complexes are the sulfur analogous of oxo-arsenicals where the arsinoyl (As = O) group is substituted by an arsinothioyl (As = S) (Raml et al., 2006). Changes in the speciation of thioarsenic compounds can occur depending on several factors, particularly the type of environment (oxic/anoxic), redox potential and pH of the medium, co-occurring chemical species, diversity of microbial community and concentration of oxygen (Herath et al., 2016). The main organic species of As which are capable of forming thioarsenic complexes in the presence of H_2S include monomethylarsonic acid (MMA^V), dimethylarsinic acid (DMA^V), arsenosugars, dimethylarsenoethanol (DMAE) and dimethylarsenoacetate (DMAA) (Maher et al., 2013). Methylated thioarsenic compounds have been identified in biological systems which are affected by other inorganic and organic As species such as, As(III), DMA^V, dimethylarsinous glutathione, and arsenosugars (Sun et al., 2016). Fig. 1 depicts important organic and inorganic thioarsenic compounds which have been extensively analysed and identified in the environmental and biological samples.

The formation of various thioarsenic species from arsenates ($H_nAs^VO_4^{3-}$) and arsenites ($H_nAs^{III}O_3^{n-3}$) has been experimentally proven (Beak et al., 2008; Bostick et al., 2005; Eary, 1992; Hollibaugh et al., 2005; Planer-Friedrich et al., 2007; Webster, 1990; Wilkin et al., 2003; Wood et al., 2002). Experimental research on identification of different thioarsenic species produced from As_2S_3 was begun almost three decades ago by Spycher and Reed (1989); this work revealed that thioanions formed from As_2S_3 can dominantly exist as trimers; $H_xAs^{III}S_6^{x-3}$ (x = 1–3) (Spycher and Reed, 1989); This finding was further supported by later researches (Eary, 1992; Webster, 1990). However, Mironova et al. (1990) came to an opposite conclusion suggesting that $H_2As_2S_3O^0$ is the dominant species of thioanions in a solution saturated with As_2S_3, since the solubility of As_2S_3 (orpiment) is independent from H_2S concentrations and pH (Mironova et al., 1990). It has been further found that monomeric thioanions ($H_xAs^{III}S_3^{n-3}$, $H_xAs^{III}OS_2^{n-3}$) are likely to be predominant in solutions saturated with As_2S_3 (Helz and Tossell, 2008). Nevertheless, Wood et al. (2002) observed that the chemistry of thioarsenic species is more intricate than previous findings of aforementioned studies (Wood et al., 2002). The Raman spectroscopic data indicated that more than six thioarsenite complexes may be present in alkaline solutions (7–13 pH) containing As(III) and sulfur at levels of 0.5 and 0.1 M, respectively (Wood et al., 2002).

3.2. Chemistry of thioarsenic species

Protonation of thioarsenic species plays a leading role in producing multiple protonation states, particularly 0, −1, −2 and −3 (Table 1) and the acidity of these species can vary with the substitution rate of S for oxygen atoms (Tossell, 2001; Wilkin et al., 2003). Occurrence of trivalent thioarsenic species in sulfidic solutions along with their corresponding formation constants was studied (Wilkin et al., 2003). In this study, mono-, di-, and try- nuclear thioarsenite species such as AsS_2^-, $As_2S_4S_4^{2-}$, and $H_2As_3S_6^-$ were identified in sulfidic water having sulfide concentrations of 0.1–1.0 mM (Wilkin et al., 2003). It has been reported that thioarsenites can be formed from aqueous $As(OH)_3^0$ through a ligand exchange mechanism where, –OH groups in arsenite are progressively replaced by –SH in sulfidic solutions at 25 °C (reaction 26–31) (Wilkin et al., 2003).

$$As(OH)_{3(aq)} + HS_{(aq)}^{-} + H_{(aq)}^{+} \rightleftharpoons As(OH)_2(SH)_{(aq)}^{0} + H_2O_{(l)}$$
$$\log K = 8.65 \pm 0.29 \quad (26)$$

$$As(OH)_{3(aq)} + HS_{(aq)}^{-} \rightleftharpoons As(OH)_2S_{(aq)}^{-} + H_2O_{(l)}$$
$$\log K = 3.54 \pm 0.36 \quad (27)$$

$$As(OH)_2S_{(aq)}^{-} + HS_{(aq)}^{-} \rightleftharpoons As(OH)S_{2(aq)}^{2-} + H_2O_{(l)}$$
$$\log K = 5.06 \pm 0.49 \quad (28)$$

$$As(OH)S_{2(aq)}^{2-} + HS_{(aq)}^{-} + H_{(aq)}^{+} \rightleftharpoons AsS_3H_{(aq)}^{2-} + H_2O_{(l)}$$
$$\log K = 11.78 \pm 0.89 \quad (29)$$

$$As(OH)S_{2(aq)}^{2-} + HS_{(aq)}^{-} \rightleftharpoons AsS_{3(aq)}^{3-} + H_2O_{(l)}$$
$$\log K = 3.89 \pm 0.41 \quad (30)$$

$$AsS_3H_{(aq)}^{2-} + HS_{(aq)}^{-} + 2H_{(aq)}^{+} \rightleftharpoons As(SH)_{4(aq)}^{-}$$
$$\log K = 16.16 \pm 0.29 \quad (31)$$

On the other hand, the occurrence of thioarsenates in strongly reducing conditions has been observed in several studies (Stauder et al., 2005; Wallschläger and Stadey, 2007). In sulfur rich As systems, under strongly reducing conditions, thioarsenates are produced through the oxidation of As(III) to As(V) without any oxidizing agent due to high affinity between As(III) and sulfur (Stauder et al., 2005). Moreover, an effort has been taken to identify four homologue (oxy)thioarsenates; AsO_3S^{3-}, $AsO_2S_2^{3-}$, $AsOS_3^{3-}$ and AsS_4^{3-} that are formed due to geochemical interactions between As(III) and sulfide in anoxic solutions (Wallschläger and Stadey, 2007). However, the findings of (Stauder

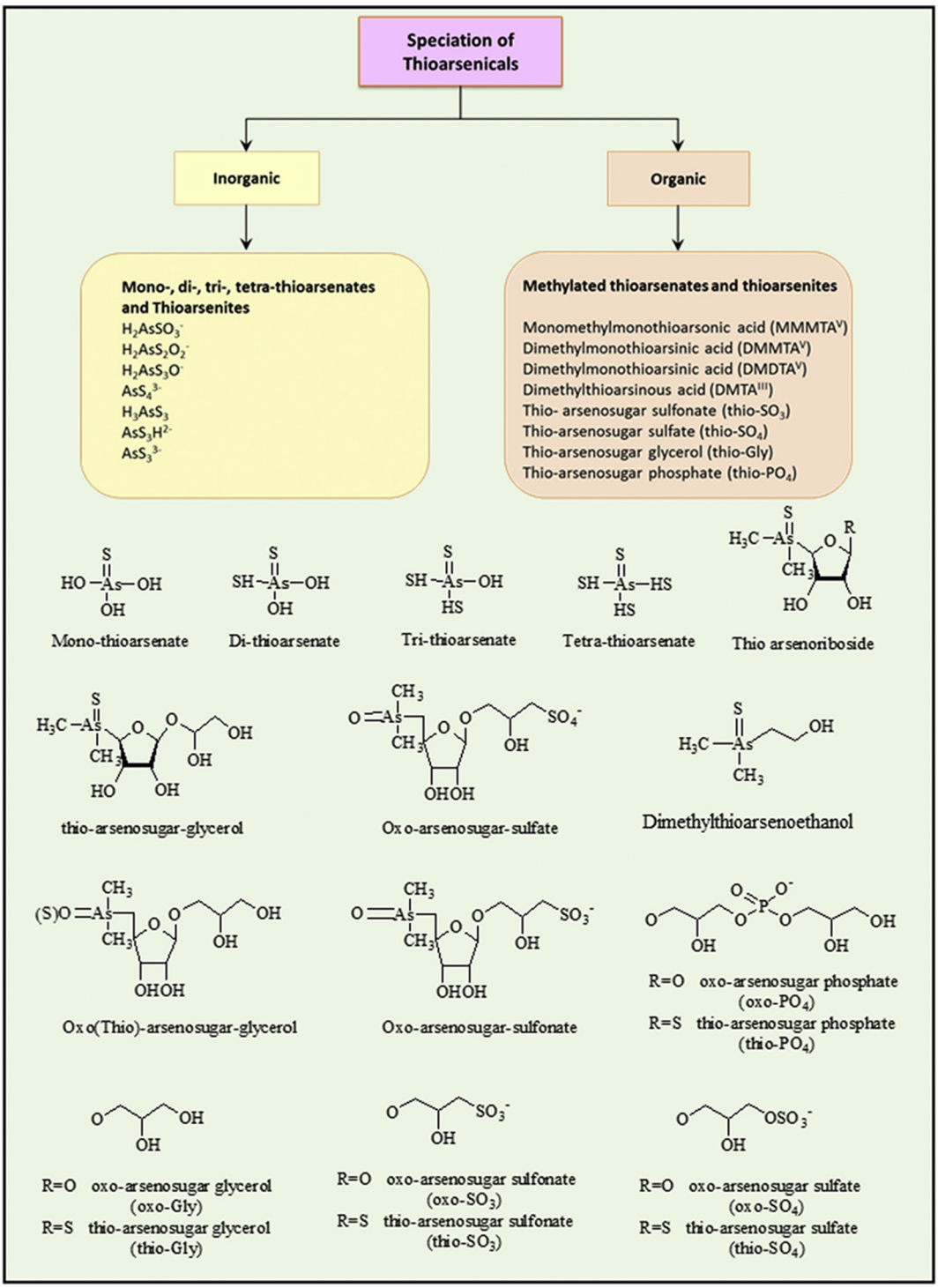

Fig. 1. Chemical speciation and structures of thioarsenic complexes which have been extensively analysed and identified in environmental, geological and biological systems.

Table 1
Different protonation states of thioarsenic species.

Charge	Thioarsenic species
0	$As(OH)_2(SH)^0$, $As(OH)(SH)_2^0$, $As(SH)_3^0$, $As(SH)_4H^0$
1-	$As(OH)_2S^-$, $As(OH)S_2H^-$, $AsS_3H_2^-$, $As(SH)_4^-$
2-	AsO_2HS^{2-}, $As(OH)S_2^{2-}$, AsS_3H^{2-}, $As(SH)_3S^{2-}$
3-	AsO_2S^{3-}, $AsOS_2^{3-}$, AsS_3^{3-}, $As(SH)_2S_2^{3-}$

et al., 2005; Wallschläger and Stadey, 2007) have now been challenged by the evidences of X-ray absorption spectroscopy (XPS and XANES) data as these techniques can be used to further confirm the formation of various thioarsenite complexes such as $AsS(SH)(OH)^-$, $As(SH)S_2^{2-}$, AsS_3^{3-} and $As(SH)^{4-}$ in sulfidic solutions under neutral to alkaline pHs and strongly reducing conditions (Beak et al., 2008; Bostick et al., 2005). The relative abundance of each thioarsenite species strongly depends on the S:As ratio and trithioarsenites become the prevailing As

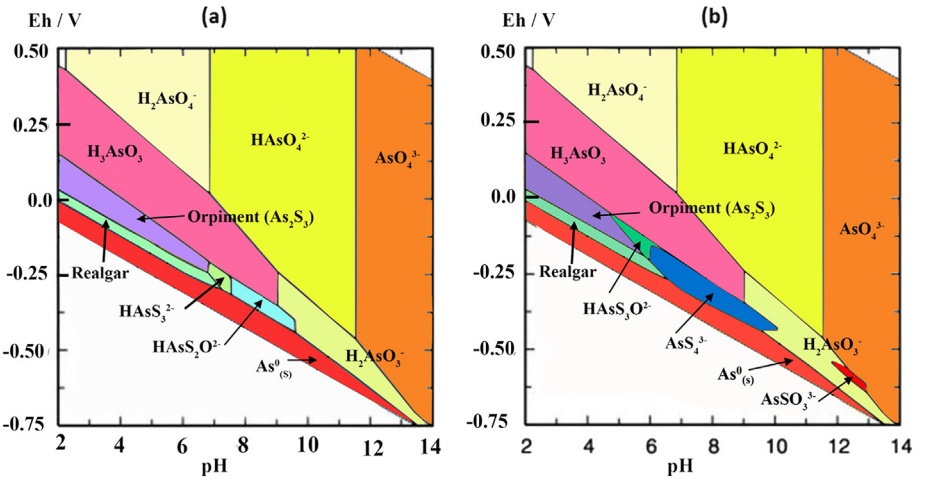

Fig. 2. Eh-pH diagrams for the (oxy)-As-S systems based on thermodynamic models proposed by (a) (Wilkin et al., 2003) (b) (Helz and Tossell, 2008) (adapted from (Hug et al., 2017)).

species when S:As ratios exceeds 3.0 in the solution (Bostick et al., 2005). This study further concluded that 40% of the total As can occur as $AsS_3S_{(3+x)}SH_{3-x}^{-x}$ complex in solutions at S:As ratios of ≥ 3 and the complexation of sulfides with As(III) is enhanced with increasing solution pH (Bostick et al., 2005).

Based on computation and empirical information on earlier thermodynamic data (Wilkin et al., 2003), a provisional model has been developed to understand the equilibrium distribution of thioarsenic species in sulfidic waters (Helz and Tossell, 2008). This model produced a thermodynamic justification for simultaneous occurrence of As(III) and As(V) thioanionic species in highly reducing sulfidic solutions, although the sulfide usually acts as a reducing agent (Helz and Tossell, 2008). The Eh-pH diagram (Fig. 2-b) shows the formation of both thioarsenates and thioarsenites as explained by (Helz and Tossell, 2008). However, such contradictory views regarding the speciation of thioarsenic anions in sulfidic environments need to be addressed by future research.

The Eh-pH diagram (Fig. 2-a) is constructed based on the thermodynamic model developed by (Wilkin et al., 2003). With regard to this model, two species of thioarsenites, $HAs(III)S_3^{2-}$ and $HAs(III)S_2O^{2-}$ are the dominant species at pH $>$ 6.25 and $>$ 7.25, respectively (Couture and Van Cappellen, 2011), whereas thioarsenate species; $HAs(V)S_3O^{2-}$ and tetrathioarsenate ($As(V)S_4^{3-}$) are dominant at pH $<$ 6 and $>$ 10, respectively as implied by the Eh-pH diagram (Fig. 2-b) proposed by Helz and Tossell (2008) (Helz and Tossell, 2008). The occurrence of deprotonated species; $As(V)S_4^{3-}$ at pH $>$ 6 is evidenced with the potential of thioanions to be more acidic than oxyanions. It is clear that monothioarsenates ($As(V)SO_3^{3-}$) possesses a small stability field at very high pH ($>$ 12). As the both diagrams imply, it is notable that the occurrence of (oxy)thioarsenic species tends to reduce the stability fields of mineral phases, such as the orpiment (As_2S_3) and realgar (AsS).

4. Occurrence and toxicity of thioarsenicals

Up to date, little information is available on the identification and quantification of thioarsenic compounds in different types of environmental and biological systems that may be due to their complexity and instability upon chemical analysis. In order to evaluate potential toxicological effects of As in the environment, it is necessary to identify and quantify a variety of thiolated-As species in natural samples. Several thioarsenic species have been identified in some environmental and biological systems, including geothermal fluids (Keller et al., 2014a; Planer-Friedrich et al., 2007; Price et al., 2010; Stauder et al., 2005), groundwater (Wallschläger and London, 2008), marine organisms (Maher et al., 2013), and human cells (Ebert et al., 2014; Raml et al., 2006; Raml et al., 2009; Raml et al., 2007). Table 2 summarizes major thioarsenic species which have been widely identified and quantified in environmental, geological and biological systems.

Most of geothermal and marine systems possess high levels of sulfur and As which lead to occurrence of thiolated-As compounds (Maher et al., 2013; Stauder et al., 2005). Microbial sulfate reduction processes can enhance the formation of thioarsenical compounds, particularly mono-, and di-thioarsenate in As-contaminated subsurface environments (Burton et al., 2013; Sun et al., 2016). Sulfate reducing bacteria may play a crucial role in the formation of thioarsenic compounds as sulfides can be produced and accumulated by bacteria in many environmental systems (Burton et al., 2013; Couture et al., 2013; Deplancke et al., 2000). Fig. 3 is a graphical representation of the cyclic of thioarsenic compounds over different compartments of the natural environment.

4.1. Occurrence of thioarsenic species in biological systems

Very limited studies have been found to be in analysing and identifying different thiolated As compounds in biological samples such as hair, nails, blood, urine and saliva due to exposure of As through dermal, respiratory and digestive systems (Table 2) (Chen et al., 2013b; Sun et al., 2016). Urine has been recognized as one of the most important biological indicators of As speciation because it is the leading pathway of As excretion in biological systems (Marchiset-Ferlay et al., 2012). In recent studies, methylated thioarsenate compounds, including dimethylmonothioarsinic acid ($DMMTA^V$) and dimethyldithioarsinic acid ($DMDTA^V$) have been detected in urine samples due to chronic exposure of As via drinking water or ingestion of arsenosugars (Mandal

Table 2
Thioarsenic compounds which have been widely detected in environmental, geological and biological systems.

Country/region	Environment	Total As concentration	Thioarsenic species	Concentrations of thioarsenic	Environmental conditions	Analytical technique	Reference
Waiotapu, New Zealand	Marine biota	13–497 μg/g	Thio-SO_3-riboside Thio-PO_4-riboside Thio-OSO_3-riboside Thio-Gly-riboside	0.06–9.1 μg/g 0.06–1.0 μg/g 0.03–0.12 μg/g 0.04–1.38 μg/g	pH 3–6	HPLC-ICPMS	(Maher et al., 2013)
	Geothermal springs	–	Mono, -di-, tri-thioarsenates	Qualitative analysis	pH 2.2–6.9 Eh 200–50 mV [H_2S] 0.58–13.33 mg/L		
South and southwest Iceland	Geothermal springs	7–116 μg/g	Mono, −di-, tri-thioarsenates	Qualitative analysis	pH 8.56–9.60 [H_2S] < 0.01–77.6 mg/L	IC-HGAFS	(Keller et al., 2014a)
Rehai, China	Geothermal water	197 < 1350 μg/L (pH 6.9–10.0) < 32.3 μg/L (pH 1.4–2.7)	Monothioarsenate Dithioarsenate	0–305 μg/L 0.23–349 μg/L	pH 1.4–10.0 [H_2S] 0.00–5.90 mg/L T 41.6–96.0 °C	AEC-ICPMS	(Guo et al., 2017)
Yellowstone National Park, USA	Geothermal Water	> 10,000 μg/g	Monothioarsenate Dithioarsenate Trithioarsenate Tetrathioarsenate	180–280 μg/L 350–550 μg/L 100–500 μg/L 0–50 μg/L	pH 2.1–9.3 [H_2S] 0.01–4 mg/L	AEC-ICPMS	(Planer-Friedrich et al., 2007)
Unspecified	Groundwater collected from an aquifer impacted by methylated As pesticides	–	Monomethylmonothioarsenate Monomethyldithioarsenate Dimethylmonothioarsenate Dimethyldithioarsenate	3.9–43.1% 0.6–15.1% 0.5–10.8% 0.4–9.0%	pH 6.5–9.5	AEC-ICPMS	(Wallschläger and London, 2008)
The Medical University of Graz, Austria	Human urine	850–1100 μg/L	Thio-Gly-riboside Thiodimethylarsinoylethanol Dimethylthioarsinate	2–8 μg/L < 75 μg/L < 130 μg/L	–	HPLC-ICPMS	(Raml et al., 2009)
	Human blood serum	3–14 μg/L	Thio-dimethylarsinoylethanol and dimethylthioarsinate	Qualitative analysis		HPLC-ICPMS	
Bangladesh	Human urine (women)	8–1034 μg/L	Dimethylthioarsinate	24–123 μg/L	–	HPLC-ICPMS	(Raml et al., 2007)
West Bengal, India	Human urine Human nails	–	Dimethyldithioarsenate Dimethylthioarsenate Dimethylthioarsenate Dimethyldithioarsenate	 Qualitative analysis	–	SEC-HPLC-ICPMS	(Mandal et al., 2008)
–	Human red blood cells	15 μg/L	Dimethylmonothioarsenate	Qualitative analysis	T 37 °C	HPLC-ICPMS	(Naranmandura and Suzuki, 2008)
–	Human cell lines in Darinaparsin		Dimethyl-arsinothioyl glutathione Dimethyl-arsinodithioic acid	Qualitative analysis	37 °C in a humidified atmosphere	HPLC-ICPMS	(Stice et al., 2016; Yehiayan et al., 2011)
China	Human urine, Human saliva	31.2–237.5 μg/g 1.5–8.0 μg/g	Thio-dimethylarsenoethanol	4.8–39.5 μg/g not detected	18 h after chinese seaweed consumption	HPLC-ICPMS	(Wang et al., 2015)
North Ronaldsay, Scotland	Sheep urine	–	Thio-dimethylarsenoacetate	Qualitative analysis	–	HPLC-ICPMS	(Hansen et al., 2004a)
New South Wales Australia	Marine macroalgae species	1.1–120.4 μg/g	Thio-SO_3-riboside Thio-OSO_3-riboside	0.06–0.17 μg/g < 0.027 μg/g	–	HPLC-ICPMS	(Foster and Maher, 2016)
–	Cabbage plants	–	Dimethylarsinothioyl glutathione	Qualitative analysis	Hydroponic system treated with dimethylarsinic acid	HPLC- ESI-MS/MS	(Raab et al., 2007)
–	Marine shellfish	–	Sulfur analogue of 2,3-dihydroxypropyl-5-deoxy-5-dimethylarsinoyl-β-D-riboside	Qualitative analysis	H_2S: As ratio 200:1 pH 3–5	IC-ICPMS and IC-ESIMS/MS	(Conklin et al., 2006)

HPLC-ICPMS: High performance liquid chromatography inductively coupled plasma mass spectrometry. IC-HGAFS: Ion chromatography hydride generation atomic fluorescence spectrometry, AEC-ICPMS: anion-exchange chromatography inductively coupled plasma mass spectrometry, SEC-HPLC-ICPMS: Size-exclusion column compared to anion exchange column coupled with HPLC-inductively coupled argon plasma mass spectrometer, ESIMS/MS: Electrospray ionization mass spectrometry.

et al., 2008; Raml et al., 2007). The levels of $DMMTA^V$ in urine samples of As-exposed women in Bangladesh were reported to be ranging from trace levels to 123 μg/L (Raml et al., 2007). A similar study reported that after ingestion of arsenosugar compounds, the $DMMTA^V$ was found in the urine of male Japanese (Raml et al., 2005). In animal based experiments, using hamsters and rats treated with a single oral dose of inorganic As(III), $DMMTA^V$ and $DMMTA^V$ were identified in the urine of hamsters, whereas the urine samples of rats contained $DMMTA^V$ and monomethylmonothioarsonic acid ($MMMTA^V$) as As metabolites (Naranmandura et al., 2007; Suzuki et al., 2010). In animal based experiments, using hamsters and rats treated with a single oral dose of As (III), $DMMTA^V$ and $DMDTA^V$ were identified in the urine of hamsters, whereas the urine samples of rats contained a mixture of $DMMTA^V$ and $MMMTA^V$ as As metabolites (Naranmandura et al., 2007; Suzuki et al., 2010).

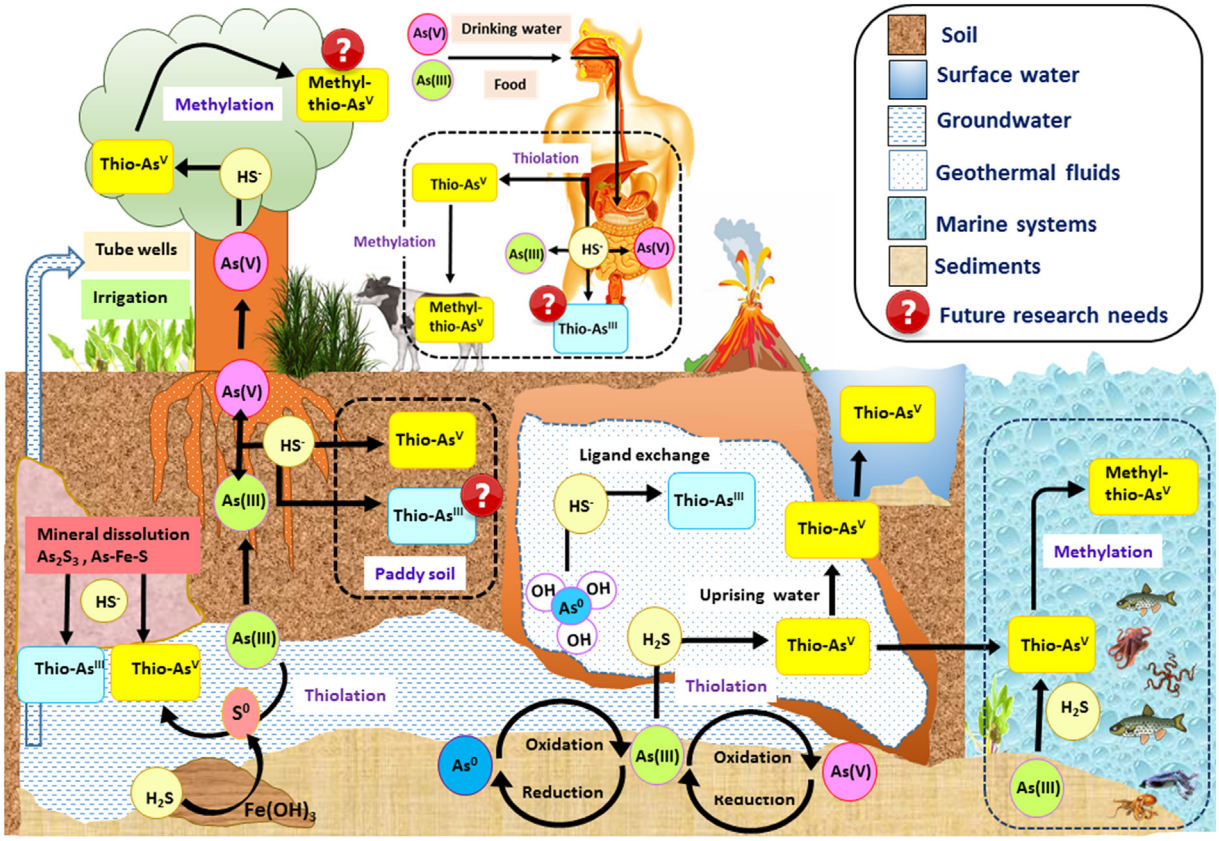

Fig. 3. Graphical representation of the transformation of thioarsenic complexes through environmental, geological and biological systems.

Apart from the occurrence of thioarsenicals in urine, various thioarsenic complexes have also been detected in blood samples of both human and animals. The occurrence of different types of methylated thioarsenic compounds was identified in human and rat red blood cells in the presence of sulfide ions (Naranmandura and Suzuki, 2008). This study found that the dimethylarsinous acid (DMA^{III}) absorbed by the red blood cells of rats can remain in the red blood cells, whereas in human red blood cells, it tends to be directly converted into MMMTA^V. Furthermore, DMMTA^V and MMMTA^V were detected in the plasma and red blood cells of female rats as a metabolite (Chen et al., 2013b). It has been reported that DMMTA^V and DMDTA^V can be dispersed in liver and kidney supernatants, urine, plasma and red blood cells of rats after intravenous injection of thioarsenicals at a dose of 0.5 mg/kg body weight (Suzuki et al., 2007).

The presence of thioarsenic compounds in some other biological systems of animals including, nail, hair and saliva has been reported in few previous studies (Chen et al., 2013a; Ponomarenko et al., 2014; Wang et al., 2015). Some sulfur-bound trivalent As compounds have been identified in human nails by X-ray absorption fine structure spectra (Ponomarenko et al., 2014). A study based on the analysis of excretion patterns of As and its metabolites in human saliva detected two thioarsenic compounds; oxo-dimethylarsinoylethanol and dimethylthioarsenoacetate in the saliva after ingestion of Chinese seaweed (Wang et al., 2015). Moreover, (Yehiayan et al., 2014) identified dimethylarsinothioyl glutathione in cellular extracts of dimethyarsinous glutathione treated human multiple myeloma cell lines (Yehiayan et al., 2014). On the other hand, the occurrence of thioarsenicals in other living organisms such as cabbages and marine molluscs, macroalgae and herbivorous animals has been confirmed by previous studies (Conklin et al., 2006; Foster and Maher, 2016; Raab et al., 2007). A complex of dimethylarsinothioyl glutathione was identified in cabbage plants grown in a hydroponic system treated with DMA^V (Raab et al., 2007). A thio-arsenosugar compound which is the sulfur analogue of As (2,3-dihydroxypropyl-5-deoxy-5-dimethylarsinoyl-β-D-riboside) was detected and quantified in marine shellfish species by which 90% of arsenosugar was converted to the analogous thio-arsenosugar complex at 3–5 pH (Conklin et al., 2006). It should be noted that the majority of previous studies is limited to a qualitative analysis of these thioarsenic compounds, since the quantification of various As species in environmental and biological matrixes is often a challenging task. Therefore, future research should be more inclined towards the quantification of thioarsenic species in a variety of environmental, geochemical and biological systems.

4.2. Toxicological effects of thioarsenic compounds

Although thioarsenic species are considered as the major As species in sulfidic-As systems, little information is available so far regarding their toxicological effects in human as well as in natural ecosystems. As the first attempt in studying the toxic effects of thioarsenates, it was reported that the acute toxicity of mono-, di-, and tri-thioarsenates to the bioluminescent bacterium (*Vibrio fischeri*) and their luminescence is significantly decreased with increasing the number of thiol groups (-SH) (Planer-Friedrich et al., 2008). This study demonstrated that mono- and di-thioarsenate are much less toxic causing a 50% decrease in luminescence of *Vibrio fischeri*, whereas the toxicity of trithioarsenate (EC50, 14.4 mg/L) is 50- and 11-fold higher than that of mono- and di-thioarsenate, respectively. It is further revealed that the toxicity of thioarsenates to *Vibrio fischeri* increased with contact time which is likely to be due to lack of a detoxification mechanisms to transform thioarsenic species into relatively less toxic oxyanions.

Inorganic As species are specifically human carcinogenic and ingested inorganic As can be bio-transformed and excreted dominantly as monomethylarsonate (MMA^V) and DMA^V (Raml et al., 2007). It is reported that humans tend to excrete constant ratios of 10–30% inorganic As, 10–20% MMA^V and 60–80% DMA^V and DMA^{III} occurs as an

intermediate in the formation of MMA^V and DMA^V (Vahter, 2002). Molecular mass spectroscopic data confirmed the formation of a DMA^{III} compound, namely dimethylarsinothioic acid ($Me_2As(=S)OH$) in urine which is further detected and identified in sheep urine samples as a metabolite (Hansen et al., 2004b).

The harmfulness of both inorganic and organic trivalent As species tends to be increased when they interact with sulfhydryl groups of some biomolecules, including glutathione, lipoic acid and the cysteinyl residues of many enzymes, thereby converting into toxic thioarsenic complexes in living organisms (Aposhian and Aposhian, 2006). The formation of thioarsenic complexes having As(III)-sulfur in living organisms, including human and animal cells may cause the inhibition of the activities of enzymes such as glutathione reductase, glutathione peroxidases, thioredoxin reductase, and thioredoxin peroxidase (Chang et al., 2003; Sharma and Sohn, 2009). The high toxicity of MMA^{III} compared to inorganic As(III) in biological systems is mainly due to its high affinity towards thiol ligands, thereby forming the monomethyl As (III)-thiolate complexes which is extremely feasible compared to inorganic As(III)-thiolate complexes (Spuches et al., 2005). Moreover, dimethyl As(III)-thiolate complexes have been found to be in sulfur-rich proteins in red blood cells of human and animals such as rat, hamster, and mouse (Shiobara et al., 2001).

In contrast to both inorganic and organic trivalent As, pentavalent As species (inorganic/organic) do not easily form complexes with sulfhydryl groups to create thioarsenate complexes, which is a positive phenomenon interestingly prevent causing toxicological effects in biological systems (Suzuki et al., 2008). However, some previous studies have found that methylated pentavalent As is capable of binding with sulfhydryl groups of biomolecules such as glutathione (GSH) to form methylated pentavalent thioarsenate complexes, including $MMMTA^V$, $MMMTA^V$, $DMMTA^V$ and $DMDTA^V$ (Fig. 3) (Bu et al., 2011; Naranmandura et al., 2007; Raab et al., 2007; Raml et al., 2007; Yoshida et al., 2003). The $DMMTA^V$ has been recognized as the most cytotoxic urinary metabolites of As which directly affects the bladder cancer cell line and thereby causing mutagenesis through the damage of DNA (Naranmandura et al., 2007; Raml et al., 2007). The human bladder is considered as the one of major target organs for highly toxic methylated thioarsenicals as As metabolites which can directly involve in the carcinogenesis (Naranmandura et al., 2011). For instance, after the exposure of human bladder cells to several As species (As (III), As(V), DMA^V, DMA^{III}, $DMMTA^V$, $MMMTA^V$, MMA^V and DMA^V), the $DMMTA^V$ induced a significant DNA damage due to the generation of extreme levels of highly reactive intracellular oxygen species (hydroxyl radical) as well as the inhibition of DNA repair proteins (p53) downstream proteins (p21) (Naranmandura et al., 2011). The $DMMTA^V$ taken by cells can be hydroxylated into DMA^V and the produced intracellular DMA^V directly involves in the damage of DNA in urinary bladder cells. With regard to the proposed mechanisms which trigger the cytotoxicity of $DMMTA^V$, the intracellular DMA^V initiates in DNA damage by the production of highly reactive intracellular oxygen species and the reduction of intracellular GSH concentrations through the redox conversion between hydroxylated DMA^V and DMA^{III}. It has been reported that $DMMTA^V$ is the most toxic As metabolite possessing similar toxicity effects as DMA^{III} and the order of cytotoxicity in bladder cancer cells is $DMA^{III} = DMMTA^V > As(III) > As(V) > MMMTA^V > MMA^V > DMA^V$ (Naranmandura et al., 2011). Similarly, $DMMTA^V$ detected in human bronchial epithelial cells was found to be highly cytotoxic and its toxicity was much higher than that of inorganic As(III) (Chilakapati et al., 2010).

A highly cytotoxic sulfur-containing As metabolite was detected in urine after a long-term oral application of DMA^V to rats (Yoshida et al., 2003). This study found that an unidentified thioarsenic metabolite is formed through the reduction of DMA^V to more toxic DMA^{III} by *Escherichia coli* bacteria and eventually excreted into the urine thereby causing carcinogenesis in urinary bladder cells (Yoshida et al., 2003). However, even after an oral administration of non-absorbable antibiotics such as gentamicin, vancomycin and nystatin to rats, $MMMTA^V$ and $DMMTA^V$ were detected in urine as a result of enterohepatic circulation suggesting that these methylated thioarsenic compounds tend to metabolize in liver and blood cells (Bu et al., 2011). During this process, the MMA^V excreted from bile is converted by gastrointestinal microbiota into $MMMTA^V$ and $DMMTA^V$ which will then be absorbed into the blood and eventually excreted into the urine (Bu et al., 2011). Moreover, the interactions between intracellular GSH and $DMMTA^V$ can particularly enhance the production of cytotoxic intermediate metabolites which may play a specific role in the carcinogenesis induced by As species in human and animal cells (Kurosawa et al., 2016; Ochi et al., 2008; Shimoda et al., 2015). The reaction between $DMMTA^V$ and GSH involves in the production of dimethylmercaptoarsine (DMA^{III}-SG) and $DMDTA^V$ through a series of reaction pathways (Kurosawa et al., 2016). Firstly, a complex of $DMMTA^V$-SG is formed from the reaction of $DMMTA^V$ with GSH and subsequently one arsenic atom is combined with one molecule of GSH. Then, the $DMMTA^V$-SG is converted into DMA^{III}-SH in the presence of excess GSH. Finally, the produced DMA^{III}-SH gets oxidized to more toxic DMA^{III} while producing H_2S which further reacts with $DMMTA^V$ to produce $DMDTA^V$. Therefore, it is clear that the cytotoxicity of $DMMTA^V$ depends not only on the formation of DMA^{III} but also on the generation of H_2S and dimethylmercaptoarsine (DMA^{III}-SH) (Kurosawa et al., 2016; Naranmandura et al., 2008). However, the $DMMTA^V$ may be detoxified by oxidative desulfuration while converting highly toxic $DMMTA^V$ into relatively less toxic DMA^V and the detoxification mechanism is mainly governed by the addition of sulfur and oxygen atoms by enzymes such as rhodanese and monooxygenase, respectively (Shimoda et al., 2015). Hence, the metabolic transformation of less toxic DMA^V from DMA^{III} and $DMMTA^V$ would be a great phenomenon to reduce the toxicological effects associated with DMA^{III} in human and animal organs. However, a compressive investigation will be essential in future research in order to prove whether the cytotoxicity effects of $DMMTA^V$ are fully associated with the metabolic production of DMA^{III}. Furthermore, it is noteworthy to mention that the most of previous studies have been more inclined towards studying the formation and toxicological effects of limited number of thioarsenic species in biological systems. Therefore, more future research on toxicity tests of numerous thioarsenic complexes via in-vitro and in-vivo experiments is an urgent necessity to understand their actual consequences in different environmental suits.

5. Chemical analysis and characterization of thioarsenicals

Accurate identification and quantification of thioarsenic species in different matrixes is entirely dependent on the analytical method selected in a certain study. In the recent decades, various instrumental methods have been developed and improved to quantify thioarsenic compounds. The speciation of thioarsenicals has been extensively accomplished by liquid and ion chromatography interfaced with inductively coupled plasma mass spectrometry (ICPMS) (Table 2). Extraction, separation and detection are considered to be the critical steps in the analysis of thioarsenic compounds (Fig. 4).

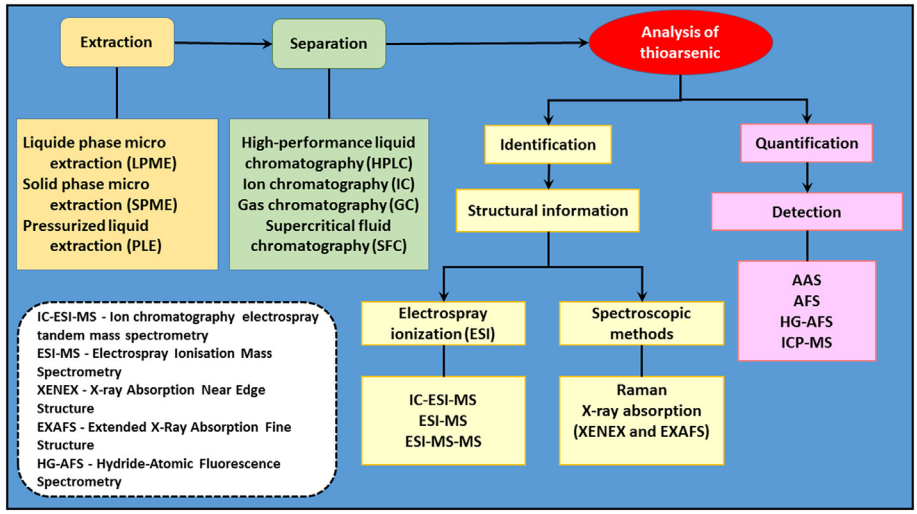

Fig. 4. An overview of identification and quantification of thioarsenic compounds in environmental and biological samples.

5.1. Extraction

Extraction is known as one of the key steps in the speciation of As by which various As compounds are released from sample matrix to an extraction media. Different extraction methods such as solvent extraction, accelerated solvent extraction, liquid phase micro-extraction, high pressure liquid extraction and solid phase micro-extraction have been used in previous studies to identify and quantify various As species, including thioarsenicals present in biological and environmental samples (Geng et al., 2009; Jiang et al., 2009; Planer-Friedrich et al., 2006; Sanz et al., 2007; Vela et al., 2001). In a previous study, As species, including thioarsenicals were extracted with water-methanol mixture from marine seaweeds and animal tissues (Kirby and Maher, 2002). Speciation of volatile thioarsenic compounds in geothermal gases of the Yellowstone National Park was carried out by using a solid-phase micro-extraction method and followed by a GCMS to identify and quantify the extracted As species (Planer-Friedrich et al., 2006). In this study, dimethylarsenomercaptane ($(CH_3)_2AsSCH_3$) was detected in geothermal gases of the Yellowstone National Park (USA) and it was identified for the first time under natural conditions. The $DMMTA^V$ was extracted and synthesised from a mixture of ethyl acetate and aqueous solution of H_2S by following a solvent extraction method (Raml et al., 2006). A new method based on the solid phase extraction was developed to separate mono-di- and tri-thioarsenates from iron-rich sulfidic waters. This study investigated that 98–100% of mono- and tri-thioarsenate species can be retained on the anion-exchange resin (AG2-$\times$8), while eluting 100% of cationic iron and thereby presenting a feasible As preservation technique for iron-rich sulfidic water samples (Druschel et al., 2003). Moreover, different As species from urine and blood samples of human and animals can be extracted by using the solutions of water-methanol and Tris-HCL buffer while gaining great recoveries of each As species (Naranmandura et al., 2010; Raml et al., 2009; Šlejkovec et al., 2008). The extracted and concentrated As species from sample matrix are always subjected to certain chromatographic and spectroscopic method in order to separate and identify corresponding species (Fig. 4).

5.2. Separation

Arsenic species can be separated out by using various separation techniques, including ion chromatography (IC), high performance liquid chromatography (HPLC), gas chromatography (GC), capillary electrophoresis (CE) and supercritical fluid chromatography (SFC) (Sun et al., 2016). Speciation of As-sulfur compounds present in environmental, biological and geochemical samples is widely performed by IC and HPLC chromatographic methods (Table 2) (Maher et al., 2013; Planer-Friedrich et al., 2014; Raml et al., 2006; Suess et al., 2015; Suess and Planer-Friedrich, 2012; Wallschläger and London, 2008). Different modes of HPLC such as ion-exchange, reverse-phase and ion-pairing methods are applied for an efficient separation of thioarsenicals from the sample matrix. Table 3 summarizes different types of columns and their conditions which have been applied in the separation of thioarsenic compounds in environmental and biological samples. The separated thioarsenic species can be detected and quantified with external calibration against thioarsenic standards by ICPMS that is coupled with a certain chromatographic system.

5.3. Detection

Detection can be known as the brain in the analysis of thioarsenic species. Atomic absorption spectrometry (AAS), atomic fluorescence spectrometry (AFS), inductively coupled plasma mass spectrometry (ICPMS) and electrospray ionization mass spectrometry (ESMS) are the most common techniques which have been widely applied for the detection and quantification of thioarsenic species in environmental, geological and biological samples (Table 3). Although the ICPMS is frequently used for the determination of total concentration of particular As compound, the combination of ICPMS with a certain chromatographic method, such as high performance liquid chromatography (HPLC), ion chromatography (IC), and gas chromatography (GC) will provide a powerful analytical tool for the identification and quantification of different chemical forms As (Popp et al., 2010). Therefore, complementary hyphenated techniques, such as HPLC-hydride generation (HPLC-HGAFS) and HPLC-ICPMS have been recognized as more reliable and sensitive analytical tools in order to determine the concentration of different thioarsenic species (Hug et al., 2017; Keller et al., 2014a; Keller et al., 2014b). The ICPMS coupled to a chromatographic system of HPLC/IC is the prevailing and selective detector for the analysis of various thioarsenic compounds with an excellent detection limit and a wide linear analysis range (ng/L–mg/L range) (Table 3) (Sun et al., 2016).

The simplicity and straight forward interface in combining the HPLC and ICPMS together are the main advantageous features of using this technology for the speciation analysis. Furthermore, a regulation of temperature over the interface between HPLC and ICPMS is not required throughout the analysis as the separation of constituents is often taken place in the HPLC at room temperature or slightly elevated temperatures (30–40 °C) (Popp et al., 2010). However, it has been

Table 3
Detailed information regarding the instrumental methods and conditions that have been applied for the analysis of thioarsenic species in different sample matrixes.

Thioarsenic species	Sample matrix	Chromatographic method	Mode of chromatography	Column conditions	Mobile phase conditions	Detector	Reference
Mono, -di-, tri-thioarsenate	Hot spring water, marine organisms and geothermal waters	HPLC	Ion exchange	Anion exchange (IonPac, AS16, 250 mm × 4 mm)	Eluent - NaOH, Gradient flow - 1-100 mM Flow rate - 1.0 mL/min	ICPMS	(Härtig and Planer-Friedrich, 2012; Hug et al., 2017; Maher et al., 2013)
Monomethylmonothio-arsenate Dimethylmonothioarsenate Dimethyldithioarsenate		HPLC	Reversed phase	Atlantis dC18 (150 mm × 4.6 mm, 5 µm)	20 mM ammonium phosphate buffer at pH 3 Flow rate - 1.0 mL/min	ICPMS	
Arsenic-thiol and methylarsonic acid-thiol complexes	Roots and shoots of rice plants	HPLC	Reversed phase	Atlantis dC18 (4.6 × 150 mm, 5 µm)	A gradient of 0.1% (v/v) formic acid (A) and 0.1% formic acid in 20% (v/v) methanol. (0–20 min, 0–75% B; 20–30 min, 75% methanol; 30–30.10 min, 20–0% B; 30.10–35 min, 0% B).	ICPMS ESIMS	(Mishra et al., 2017)
Thio-dimethylarsinate Thio-dimethylarsenoethanol Thio-dimethylarsenoacetate Trimethyl-arsine sulfide Thio-arsenosugar glycerol Thio-arsenosugar sulfonate Thio-arsenosugar sulfate	Spiked solutions	HPLC	Reversed-phase	Atlantis dC18 (4.6 mm × 150 mm)	20 mM ammonium phosphate buffer at pH 3 Flow rate - 1.0 mL/min	ICPMS	(Raml et al., 2006)
Mono-di-try- and tetra-thioarsenates	Sulfidic water	IC	Ion exchange	Anion exchange (IonPac, AG16 + AS16, 4 mm, Dionex)	Eluent - NaOH, Gradient flow - 0.02–0.1 M flow rate - 1.2 mL/min	ICPMS	(Suess et al., 2015; Suess and Planer-Friedrich, 2012; Wallschläger and Stadey, 2007)
Monomethylarsenate, monomethylmonothioarsenate, monomethyldithioarsenate, monomethyltrithioarsenate, dimethylmonothioarsenate, dimethyldithioarsenate	Groundwater	IC	Ion exchange	Anion exchange (Ion Pac) (AG-16 + AS-16 4-mm, Dionex)	Eluent - NaOH, Gradient flow - 20-100 mM Flow rate - 1.2 mL/min	ICPMS	(Wallschläger and London, 2008)
Dimethylmonothioarsenate, dimethyldithioarsinate		HPLC	Normal phase	Polymer-based gel filtration column (GS 220 HQ, 300 mm × 7.6 mm)	Eluent - Ammonium acetate buffer Gradient flow - 50 mM Flow rate - 0.6 mL/min	ICPMS	(Suzuki et al., 2007)
Thioarsenite, mono-di-try- and tetra-thioarsenates		IC	Ion exchange	Anion exchange (IonPac AS16 4 × 250 mm, Dionex)	Eluent - KOH Gradient flow - 20-100 mM flow rate - 1.0 mL/min	HGAFS	(Keller et al., 2014a, 2014b)
Thio-arsenoribosides		HPLC	Reversed-phase	Atlantis dC18 (150 mm × 4.6 mm, 5 µm)	Eluent - ammonium phosphate and phosphoric acid buffer Gradient flow - mM flow rate - 1.0 mL/min	ICPMS	(Foster and Maher, 2016)
Thio-arsenosugar-sulfonate Thio-arsenosugar-sulfate		HPLC	Ion exchange	Anion exchange (Hamilton PRP-×100, 150 mm × 1.0 mm, 5 µm)	Eluent - ammonium bicarbonate and 55% methanol Gradient flow – 20 mM flow rate – 30 mm^3/min	EISMS	(Kahn et al., 2005)
Dimethyl-thioarsenic sulfonate Dimethyl-thioarsenic sulfate	Marine molluscs	HPLC	Reverse phase anion pairing	Anion exchange (Hamilton PRP-×100, 250 × 4.1 mm)	Eluent - ammonium bicarbonate and 5–40% methanol Gradient flow – 20 mM Flow rate – 1 mL/min	EISMS ICPMS	(Nischwitz et al., 2006)

(*continued on next page*)

Table 3 (*continued*)

Thioarsenic species	Sample matrix	Chromatographic method	Mode of chromatography	Column conditions	Mobile phase conditions	Detector	Reference
Thio-dimethylarsinate	Human urine	HPLC	Ion exchange	(i) Anion exchange (Hamilton PRP-×100 (1 × 150 mm)) (ii) Atlantis dC18 column (4.6 × 150 mm, and 1 × 150 mm	Eluent - ammonium bicarbonate and 10% methanol Gradient flow - 10 mM flow rate - 100 μL/min Eluent - ammonium formate and 10% methanol Gradient flow - 5 mM flow rate - 20 μL/min	EISMS ICPMS	(Raml et al., 2007)
Thio-arsenosugar-glycerol	Human hepatic and urothelial cells	LC	Ion exchange	Anion exchange (Hamilton PRP-×100, 4 × 150 mm, 10 μm).	Eluent - ammonium carbonate/formic acid buffer (pH 8) Gradient flow - 20 mM flow rate - 1 mL/min	ICP-MS/MS	(Ebert et al., 2014)
Mono-, di-, tri-, and tetra-thioarsenic	Geothermal water	AEC	Ion exchange	Anion exchange (IonPac AS-16/AG-16, 4 mm)	Eluent - NaOH, Gradient flow - 0.02-0.1 M flow rate - 1.2 mL/min	ICPMS EIS-MS/MS	(Planer-Friedrich et al., 2007)

HPLC: High performance liquid chromatography; IC: Ion chromatography; LC: Liquid chromatography; AEC: Anion exchange chromatography; ICPMS: Inductively coupled plasma mass spectrometry; EISMS: Electrospray ionization mass spectrometry; HGAFS: Hydride generation atomic fluorescence spectrometry.

reported that the use of high concentrations of organic solvents, salts in buffer solutions and ion-pairing reagents as the mobile phase may lead to several negative impacts, including a signal suppression, peak broadening, and blockage of the nebulizer, injector or sampling cone (Michalke, 2002). Hence, it is highly recommended to use diluted buffers as the mobile phase for the speciation analysis performed with ICPMS. Nevertheless, the concentration of buffers used in IC systems is frequently higher than 0.1 mol/L which may cause aforementioned drawbacks in the analysis process. Meanwhile, the characterization of species that are separated and detected by HPLC-ICPMS is a vital point in order to identify the molecular structure of unknown species present in the sample matrix.

5.4. Characterization of thioarsenic compounds

State-of-the-art spectroscopic methods, such as Raman, electrospray ionization mass spectrometry (EISMS), and X-ray absorption spectroscopy (XAS) have been applied in several previous studies to propose/confirm the molecular structure of thioarsenic compounds (Burton et al., 2013; Nischwitz et al., 2006; Planer-Friedrich et al., 2007; Raml et al., 2007; Suess et al., 2009; Xiao et al., 2015). The structure of unknown thioarsenic species appearing in HPLC-ICPMS chromatograms can be postulated by EISMS data (Nischwitz et al., 2006; Planer-Friedrich et al., 2007). An advanced analytical set up of HPLC-ICPMS coupled simultaneously to HPLC-ESMS identified the structure of a new As metabolite, namely dimethylarsinothioic acid ($Me_2As(=S)OH$) in urine and wool of wild sheep due to ingestion of seaweed contaminated with arsenosugars (daily intake of 35 mg of As) (Hansen et al., 2004b). A complex of dimethylarsinothioyl glutathione was recognized in As-exposed cabbage and cellular extracts of dimethyarsinous glutathione as a metabolite by a parallel use of HPLC-ICPMS and ESIMS (Raab et al., 2007; Yehiayan et al., 2014). Moreover, urine samples of rats were characterized with other types of thioarsenicals, including monomethylmonothioarsenate, dimethylmonothioarsenate, and dimethyldithioarsenate by a combination of ion chromatography (IC)-ICPMS and liquid chromatography (LC)-ICPMS with ESI-ICPMS (Adair et al., 2007; Drobna et al., 2009; Naranmandura et al., 2013). In a very recent study, HPLC coupled online to ICPMS and ESIMS in parallel have been used for the separation and identification of methylthioarsenate complexes in fresh extracts of root and shoot of rice plants (Mishra et al., 2017).

Raman spectroscopic data can be used to understand the chemical nature of S—As bonds in S-bearing As compounds which is evidence in identifying different thioarsenic species (Wood et al., 2002). Raman spectroscopic measurements obtained for aqueous chemical solutions at 25 °C and pH 7–13.2 suggested six distinct thioarsenic species having different modes of As–S–O–H bonds at band frequencies; 365, 385, 390, 400, 415 and 420 cm^{-1} (Wood et al., 2002).

Spectroscopic results obtained from advanced XAS techniques, including X-ray absorption near-edge structure (XANES) and the extended X-ray absorption fine structure (EXAFS) are capable of confirming the formation of thioarsenic compounds having As(III)-S bond length of 2.23–2.24 Å in sulfur rich-arsenite model solutions (Beak et al., 2008). A previous study based on the characterization of mono-di-and tetra-thioarsenates by XAS revealed that spectral data of these thioarsenates are significantly different from those of As(III)-sulfur species as well as arsenite and arsenate species (Suess et al., 2009). The XAS results of this study further demonstrated that the bond lengths of [As(V)-S] and [As (V)-O] (2.13–2.18 Å and 1.70 Å, respectively) in thioarsenate species are considerably shorter than those of [As(III)-S] and As(III)-O in thioarsenite species (2.24–2.34 Å and 1.78 Å, respectively) (Suess et al., 2009). Moreover, XANES and EXAFS data generated from As(III)-sulfur solutions with S:As ratios from 0.1 to 10 indicated that thioarsenites are the primary reaction products of As(III)-S solutions in the complete absence of oxygen, whereas thioarsenites are quickly oxidized to thioarsenates while getting exposed to atmospheric oxygen (Price et al., 2010). Such a rapid oxidation of thioarsenite to thioarsenates from 1 to

24 h sample exposure in an analysis using IC-ICPMS were confirmed by giving rise a clear shift in XANES edge positions from 11,869.4 to 11,869.9 eV (tri- and tetra-thioarsenate) compared to the XANES edge position of trithioarsenite (11,867.0 eV) (Price et al., 2010). Therefore, it is clear that there are direct spectroscopic analytical evidences for the existence of As-sulfur species and their chemical structures in environmental, geochemical and biological matrixes.

6. Challenges upon analysis and conservation of thioarsenicals

Accurate measurement of thioarsenic species has been indeed a challenging task due to their instability upon several matrix dependent factors, including pH, temperature, redox potential, and concentrations of oxygen, sulfur and metal impurities such as iron (Couture and Van Cappellen, 2011; Helz and Tossell, 2008; Hug et al., 2017). Therefore, the stability of thioarsenic species is the major challenging fact to be taken into consideration before performing a speciation analysis.

6.1. Stability of thioarsenic species

The oxidation behaviour of thioarsenites to thioarsenates has been studied by using an ion chromatography technique under both aerobic and anaerobic conditions (Price et al., 2010). This study found that thioarsenites are exceptionally unstable towards the oxidation in the presence of oxygen and thereby converting rapidly to thioarsenates (Price et al., 2010). As a result of that thioarsenites are often present as thioarsenates in IC analyses and this problem is always associated when the oxygen is not fully eliminated from the chromatographic system. The oxidation of thioarsenites in aerobic environments may be expressed as following reaction pathways (Hug et al., 2017).

$$2H_2AsOS^-_{3(aq)} + 5O_{2(aq)} \rightarrow 2H_2AsO_2S^-_{2(aq)} + 2SO^{2-}_{4(aq)} \quad (32)$$

$$2H_2AsO_2S^-_{2(aq)} + 5O_{2(aq)} \rightarrow 2H_2AsO_3S^-_{(aq)} + 2SO^{2-}_{4(aq)} \quad (33)$$

$$H_2AsO_3S^-_{(aq)} + H^+_{(aq)} \rightarrow H_3AsO_{3(aq)} + S^0_{(s)} \quad (34)$$

$$H_3AsO_{3(aq)} + O_{2(g)} \rightarrow H_2AsO^-_{4(aq)} \quad (35)$$

The thiol part of thioarsenic molecules can also be oxidized by sulfur-oxidizing bacteria, such as *Thioalkalivibrio jannaschii*, *Thioalkalivibrio versutus*, *Thioalkalivibrio nitratis*, etc. (reaction 36) (Fisher et al., 2008). A chemical analysis of water samples collected from Mono lake, California indicated that mono-and di-thioarsenate formed in arsenite and sulfide amended lake water are justly stable in sterile alkaline media (pH 9.8), whereas these thioarsenates tend to be converted into arsenate and sulfate in the presence of sulfur-oxidizing bacteria (Fisher et al., 2008).

$$2H_2AsO_3S^-_{(aq)} + 5O_{2(aq)} \rightarrow 2HAsO^{2-}_{4(aq)} + 2SO^{2-}_{4(aq)} + 2H^+_{(aq)} \quad (36)$$

Thioarsenates are likely to be converted into arsenate and sulfur by either a ligand exchange mechanism through which HS^- group is replaced by OH^- ions (reaction 37) or decomposition into arsenite and sulfur (reaction 38).

$$HAsO_3S^{2-}_{(aq)} + OH^-_{(aq)} \rightarrow HAsO^{2-}_{4(aq)} + HS^-_{(aq)} \quad (37)$$

$$HAsO_3S^{2-}_{(aq)} + H^+_{(aq)} \rightarrow H_2AsO^-_{3(aq)} + S^o_{(s)} \quad (38)$$

Thioarsenate species can also undergo a depletion under oxic conditions which may result in a small amount of thiolated As species and ultimately arsenite (Planer-Friedrich et al., 2007). Oxic and anoxic conditions can have an impact on the concentrations of $[SH^-]$ and $[OH^-]$ in sulfidic solutions and the stability of thioarsenic species depends on the ratio between $[SH^-]$ and $[OH^-]$ (Price et al., 2010). If $[SH^-] > [OH^-]$ under anoxic conditions, thioarsenite becomes the most stable As species, while in oxic environments, thioarsenate is the prevailing species (Hug et al., 2017; Price et al., 2010). Thioarsenic species tend to be unstable in the presence of excess OH^- and when $[SH^-] < [OH^-]$ under either oxic or anoxic conditions; then, arsenite will be the most stable species (Hug et al., 2017).

Furthermore, thioarsenites are not stable upon sample dilution and this commonly happens before a chromatographic analysis which is interfaced with ICP-MS as an ultrasensitive detector. Dilution of samples may cause the change in pH which tends to rearrange the equilibrium between individual As-sulfur species because of their distinct stability regions depending on the pH range (Price et al., 2010). On the other hand, when the pH is maintained steady during the dilution, ratio between [OH] and $[SH^-]$ may be changed in the solution, thereby shifting the primary speciation equilibria. Therefore, it is recommended to use undiluted samples when chromatographic methods interfaced with a ICPMS detector are used for the speciation of thioarsenicals.

Existence of iron in natural samples can be particularly challenging for an accurate determination of the speciation of thioarsenicals (Suess et al., 2015; Ullrich et al., 2016). In the presence of high levels of iron in sulfidic waters, the formation of thioarsenates from arsenite and sulfide becomes limited due to the precipitation of excessive sulfide as iron-sulfide minerals (Suess et al., 2015). Bednar et al. (2002) revealed that 0.3 mM of arsenite is fully oxidized to arsenate in an unpreserved sample containing 18 mM of Fe(III) (Bednar et al., 2002). On the other hand, both arsenite and arsenate can easily co-precipitate or adsorb on iron oxy-hydroxides present in sulfur-rich waters which may lose available As species for the analysis (Dixit and Hering, 2003; Herath et al., 2016). However, Suess and Planer-Friedrich (2012) showed that thioarsenates can be formed in Fe-S-As systems via oxidative dissolution of arsenopyrite at high pH (pH > 10). It has been found that thioarsenates are capable of occurring in iron-rich spring and groundwater (Burton et al., 2013; Suess et al., 2011). For instance, iron concentrations in mineral springs of Czech Republic were reported to be ranging 1.3–66 mg/L and the fraction of thioarsenates accounted for only 17% of the total As levels at relatively low sulfide concentrations (0.02–0.5 mg/L) (Suess et al., 2011). Therefore, the preservation of sample matrixes prior to chemical analysis would be a crucial stage in order achieve an accurate measurement of thioarsenic species.

6.2. Preservation of thioarsenic species

Preservation of samples of thioarsenic species is an essential step in order to understand their fate in natural systems. Interestingly, monothioarsenate is found to be the most stable thioarsenic species and it can be preserved for over 14 days without adding any stabilizing agent with a percentage recovery at 98 ± 0.4% of the total As species in the absence of iron (Suess et al., 2015). Preservation of thioarsenic species is quite a difficult task and unsuitable sample preservation methods would bring about inaccurate measurements of particular As species. Therefore, different preservation methods, including, acidification, flash-freezing, EDTA and base addition, solid phase extraction etc. have been tested in order to overcome aforementioned challenges towards the chemical analysis of samples for the speciation of thioarsenicals. Table 4 summarizes some sample preservation techniques which are recently applied for the preservation of thioarsenic species in aqueous solutions. However, kinetic and thermodynamic interpretations on the stability of different thioarsenic compounds are essential based on experimental and model data which need to be addressed by future research in order to establish appropriate preservation strategies for the speciation thioarsenicals in environmental samples.

6.2.1. Acidification

Acidification of samples using mineral acids, such as HNO_3, HCl, H_2SO_4, H_3PO_4, etc. is the most widely applied sample preservation technique for the speciation of As in iron-rich matrixes (Daus et al., 2002; Ullrich et al., 2016). This technique can be used to keep the pH of samples below 2 which may allow to preserve As species in the presence of Fe(III) at a concentration of up to 300 μM for a maximum of 6 weeks

Table 4
Sample preservation techniques and their effectiveness for the speciation of thioarsenic compounds in aqueous solutions.

Preservation technique	Matrix	Thioarsenic species	% recovery or variability	Stability	Reference
Stabilization with NaCl (absence of iron)	Synthetic solutions	Monothioarsenate	95 ± 0.3% (13 ± 1 μM)	7 days	(Suess et al., 2015)
Cryo-preservation in anoxic septum vials (absence of iron)		Trithioarsenate	71 ± 7% (11 ± 1 μM)	14 days	
Stabilization with ethanol (absence of iron) in combination with flash freezing in anoxic septum vials (absence of iron)		Trithioarsenate	76% (11 μM)	7 days	
Without any preservation additives in the presence of iron (0.09–0.9 mM)	Synthetic solutions	Monothioarsenate	91 ± 1% (10 ± 1 μM)	1 day	(Suess et al., 2015)
Cool anoxic storage at 0.09–0.9 mM of iron		Trithioarsenate	45–66%	3 days	
Cryo-preservation with 0.1 M EDTA at 0.9 mM		Trithioarsenate	52 ± 6% (6 ± 2 μM)	6 days	
Flash freezing at 4 °C		Trithioarsenate	50 ± 5% (7 ± 1 μM)	6 days	
Solid phase extraction (SPE) in the presence of iron	Spiked water	Monothioarsenate Trithioarsenate	91.9 ± 2.0 89.7 ± 3.4	–	(Ullrich et al., 2016)
Flash freezing on dry ice at −20 °C	Geothermal water	Mono-di- and tri-thioarsenates	–	5–67 days	(Planer-Friedrich et al., 2007)
Flash freezing on dry ice at −20 °C	Spring water	Mono thioarsenates Di-thioarsenates Tri-thioarsenates	7.92–9.69 μM 0.9–2.5 μM 1.17–15.3 μM	–	(Härtig and Planer-Friedrich, 2012)
Flash-freezing on dry ice with minimal anoxic headspace and cryo-storage	Mineral spring water	Mono- and tri-thioarsenate	< 3% variability in species distribution	21–42 days	(Suess et al., 2011)
Addition of NaOH (0.1 M) and EtOH with oxic headspace, flash-freezing and cryo-storage in the freezer at −18 °C	Spring water with spiked matrix solutions	Monothioarsenate Tetrathioarsenate	< 1% variability < 3% variability	13 days 21 days	
Stabilization with EDTA (0.01 M) neutralized with NaOH (pH 7) in the presence of iron		Mono- and di-thioarsenate Trithioarsenate	< 3% variability < 10% variability	7 days 7 days	
Stabilization with neutralized EDTA (0.01 M) and flash-freezing in the presence of iron		Monothioarsenate Dithioarsenates Trithioarsenate	94% recovery (< 10% variability) 68% recovery (< 10% variability) 45% recovery (~20% variability)	11 days	
Flash-freezing on liquid nitrogen at −80 °C and store in anoxic bags together with oxygen-scrubbing GasPak EZ anaerobe paper sachets	Geothermal springs	Mono, -di, and tri-thioarsenate	–	–	(Maher et al., 2013; Ullrich et al., 2016)

(Aggett and Kriegman, 1987). Nevertheless, the acidification using HCl is not recommended for sulfur-rich waters as it may lead to loss of the total amount of As via a precipitation of As sulfide (As_2S_3) (Smieja and Wilkin, 2003). In addition to that, a rapid oxidation of arsenite has been observed, when the samples are preserved with strong acids such as HNO_3 and HCl (Bednar et al., 2002). Therefore, Smieja and Wilkin (2003) proposed a method for the preservation of total As in sulfidic water (0.4 mg/L of sulfur) by developing a three-step procedure including base addition, oxidation and acidification (Smieja and Wilkin, 2003).

6.2.2. Use of chelating agents

Alternatively, EDTA has been used as a chelating agent to avoid co-precipitation of As with iron-and manganese-oxyhydroxides as well as change in As speciation by iron induced photochemical oxidation from pH buffering, iron-complexation and ligand exclusion (Gallagher et al., 2001; Gault et al., 2005; Oliveira et al., 2006; Samanta and Clifford, 2006). Bednar et al. (2002) found that acid mine drainage and groundwater samples treated with EDTA in opaque bottles can protect the water samples during 3 months while achieving (−5) - (+3)% of change in arsenite:arsenate ratios. However, it is found that the use of EDTA to preserve water samples having high levels of iron and less amounts of total As is inappropriate due to negative impacts of the oxidation state of iron on the preservation efficiency (McCleskey et al., 2004; Oliveira et al., 2006). Therefore, flash freezing that was established by (Crecelius et al., 1986) has been recognized as an effective preservation technique for the speciation of thioarsenates present in natural water systems (Hollibaugh et al., 2005; Planer-Friedrich et al., 2007).

6.2.3. Flash freezing and cryo-storage

Flash freezing and cryo-storage have been recognized as the best techniques for the preservation of As in pure sulfidic waters (Planer-Friedrich et al., 2007). However, both methods are not suitable for iron-rich sulfidic systems as they encourage the oxidation of iron, thereby co-precipitating As with iron oxihydroxides which may cause a loss of total As in the sample matrix. A characterization of sulfidic water samples collected from Mono Lake, USA demonstrated that the preservation of water samples via flash-freezing with liquid nitrogen at −196 °C can effectively recover the species of As, including mono-, di- and tri-thioarsenic in lake water samples (Hollibaugh et al., 2005). However, flash-freezing is recommended for samples having low concentrations of iron (< 5 mg/L) due to precipitation of iron in the matrix during liquid freezing (Ullrich et al., 2016). An efficient preservation can be achieved by using oxygen scrubbing sachets which may fully remove oxygen within the gas-tight sampling bags thereby minimizing the change in As speciation via oxidation.

6.2.4. Solid phase extraction

Solid phase extraction (SPE) method is found to be the best technique so far for the preservation of thioarsenic species in iron-rich sulfidic systems (Ullrich et al., 2016). Aluminosilicate and anion exchange resins are the stationary phases that are commonly used in SPE cartridges (Ficklin, 1983; Meng et al., 2001). Since thioarsenic species predominantly exist in anionic form under environmentally relevant conditions, they can retain in the anion exchange resin, while eluting positively charged iron without adsorbing on the resin. Therefore, the SPE technique prevents the change in speciation of thioarsenic compounds in the presence of iron. However, the most challenging task is the selection of a suitable eluting agent to take off the retained thioarsenic species without changing their speciation until the analysis. Some previous studies regarding speciation analyses of As and antimony in geothermal water showed that the elution of retained thioarsenic species on the cartridge is quite difficult for analysis (Lord et al., 2012; Planer-Friedrich and Wilson, 2012; Ullrich et al., 2013). It has been found that the elution with acids such as HCl and HNO_3 would

lead to change in speciation as well as As sulfide precipitation (Druschel et al., 2003). In order to overcome these issues associated with the preservation of environmental samples for As speciation analysis, a new method based on SPE has been very recently developed for the preservation for thioarsenates in iron-sulfur-water systems (Ullrich et al., 2016). In this procedure, synthetic solutions containing arsenite, arsenate, monothioarsenate, and trithioarsenate were passed through an anion exchange resin (AG2-×8) and after elution, the resin was washed in 15 mL of 0.5 M sodium salicylate ($C_7H_5NaO_3$) which achieved a retention of arsenate, monothioarsenate and trithioarsenate at 96.8 ± 0.2%, 98.8 ± 0.2%, and 99.6 ± 0.3%, respectively. Interestingly, this method performed almost 100% of elution of iron (90 mM of Fe(II)) through the resin. Furthermore, sulfur and As species retained on the resin of SPE were successfully washed and eluted by using 0.5 and 3 M of KCl and 0.5 M sodium citrate ($C_6H_5Na_3O_7$) (Druschel et al., 2003; Ullrich et al., 2016; Ullrich et al., 2013).

7. What needs to be done in future research?

Environmental consequences of thioarsenic complexes have become apparent over the recent decades. Relatively brief history of thioarsenic research mostly in the current decade, investigating the occurrence, geochemistry, speciation and toxicology has endeavored to understand their consequences in the natural environment. However, thioarsenic compounds have by far not attached much research concern on global scale compared to other inorganic and organic As species and hence, their formation mechanisms, occurrence and stability in different environmental, geochemical and biological systems are still a subject of debate. Significance of various thioarsenic species in natural systems as well as human health is of particular concern as the present review has been discussed.

This critical review has demonstrated that most of previous studies have been limited to a qualitative identification of some thioarsenic species and only little effort has been undertaken on their quantitative analysis in limited environmental matrixes. Despite the advances of qualitative understanding of thioarsenic compounds, quantitative information of thioasenicals in a variety of environmental systems, such as mine soil and water, ground-and surface-water, paddy rice ecosystems, mangrove systems, crop plants, etc. is still lacking which would beneficial to predict the hazardous consequences of As in the environment. Reporting on the distribution of thioarsenic species over global ground-surface waters has been insignificant up to date. Assessment of direct and indirect effects of toxic thioarsenic compounds on global population those who frequently exposure to high concentrations of As through drinking and irrigation water is an urgent necessity. Moreover, a significant research gap can be seen in the research on occurrence, formation mechanisms and analysis of thioarsenic complexes in As-contaminated soil systems. Kinetics and thermodynamic interpretations on mineral dissolution and formation of thioarsenic compounds are highly unknown or determined under laboratory conditions. Field scale experiments and development of models are essential for determining formation mechanisms, Eh-pH diagrams, mobilization and transformation that are critical for assessing the environmental fate and consequences of various inorganic and organic thioarsenic species. Therefore, fundamental studies based on the separation and identification thioarsenic species should need be prolonged by future research in determining the molecular structure of unknown thioarsenic complexes and their definite concentrations in a variety of environmental suites, including, ground-surface-irrigation water, soil, sediments and biological organisms. Contemporary approaches hyphenated to existing technologies would pave the way to overcome critical challenges of thioarsenic speciation such as synthesis of standards, structural determination, quantification and sample preservation in future research.

8. Conclusions

This review focusses on the existing knowledge in relation to the formation mechanisms of thioarsenic species, their chemistry, speciation and analytical methodologies in order to provide a rational assessment of what is new, what is current, what needs to be done in future research. Thioarsenic compounds are formed as a result of geochemical interactions between As and sulfur-bearing compounds (S^{2-}/HS^-) in favourably reducing or anoxic environments. Sulfur-arsenite/arsenate interactions and dissolution of arsenic sulfide minerals are the main mechanisms that involve in the formation of different thioarsenic species in the natural environment. The formation of thioarsenic complexes may lead to increase the solubility, mobility and bioavailability of As in the environment. Changes in the speciation of thioarsenic compounds can occur depending on the type of environment (oxic/anoxic), redox potential and pH of the medium, co-occurring chemical species, and diversity of microbial community. With regard to the cytotoxic effects of thioarsenicals in human and animal cells, $DMMTA^V$ is the most cytotoxic As metabolite due to the generation of DMA^{III} by the reduction of DMA^V with GSH. Extraction, separation and detection are considered as the main steps in the analysis of thioarsenic species. Raman, electrospray ionization mass spectrometry and X-ray absorption spectroscopy can be used to confirm the molecular structure of thioarsenic compounds. The analysis of thioarsenic species is a challenging task due to their instability upon pH, temperature, redox potential, and concentrations of oxygen, sulfur and iron. Solid phase extraction method has been found to be the best technique for the preservation of thioarsenicals in iron-rich sulfidic systems. More future researches are essential on thioarsenic related aspects in clarifying formation mechanisms, developing upgraded analytical instrumentation and improved preservation strategies to establish a sustainable arsenic mitigation on a global scale.

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