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Organoarsenicals in Seafood: Occurrence, Dietary Exposure, Toxicity, and Risk Assessment Considerations — A Review

Caleb Luvonga,
National Institute of Standards and Technology (NIST), Gaithersburg, Maryland, and University of Maryland, College Park, Maryland

Catherine A. Rimmer,
National Institute of Standards and Technology (NIST), Gaithersburg, Maryland

Lee L. Yu,
National Institute of Standards and Technology (NIST), Gaithersburg, Maryland

Sang B. Lee
University of Maryland, College Park, Maryland

Abstract

Diet, especially seafood, is the main source of arsenic exposure for humans. The total arsenic content of a diet offers inadequate information for assessment of the toxicological consequences of arsenic intake, which has impeded progress in the establishment of regulatory limits for arsenic in food. Toxicity assessments are mainly based on inorganic arsenic, a well-characterized carcinogen, and arsenobetaine, the main organoarsenical in seafood. Scarcity of toxicity data for organoarsenicals, and the predominance of arsenobetaine as an organic arsenic species in seafood, has led to the assumption of their nontoxicity. Recent toxicokinetic studies show that some organoarsenicals are bioaccessible and cytotoxic with demonstrated toxicities like that of pernicious trivalent inorganic arsenic, underpinning the need for speciation analysis. The need to investigate and compare the bioavailability, metabolic transformation, and elimination from the body of organoarsenicals to the well-established physiological consequences of inorganic arsenic and arsenobetaine exposure is apparent. This review provides an overview of the occurrence and assessment of human exposure to arsenic toxicity associated with the consumption of seafood.

Keywords

arsenic; speciation; toxicity; carcinogen; exposure; seafood; organoarsenicals

1. INTRODUCTION

It is estimated that the ocean is inhabited by more than 1000 species of crustaceans and 50000 species of mollusks, aside from the 13000 species of finfish.[1] Marine species

Corresponding Author: **Caleb Luvonga** - National Institute of Standards and Technology (NIST), Gaithersburg, Maryland, and University of Maryland, College Park, Maryland; luvonga@gmail.com.

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including seafood and seaweed are deemed as essential portions of healthy diets as they comprise various nutrients linked with beneficial health effects[2] and are widely used as dietary supplements. Human consumption of seafood has been increasing steadily mainly because of the reports of health benefits associated with their consumption.[2–4]

Like all mammals, humans lack enzymes for the synthesis of omega-3 (ω-3) and omega-6 (ω-6) precursors of DHA and EPA, which are therefore essential fatty acids and need to be provided by dietary sources.[5] Fish is the best dietary source of protein, long-chain omega-3 polyunsaturated fatty acids (ω-3 LCPUFAs) and other nutrients which are linked to a range of health benefits.[6] Long-chain omega-3 polyunsaturated fatty acids (ω-3 LCPUFAs), particularly eicosapentanoic acids (EPA, 20:5ω-3) and decosahexanoic acid (DHA, 22:6ω-3), have been demonstrated to have antiatherosclerotic and antithrombotic effects[3] and are linked to reduced risk of cardiovascular disease (CVD).[7] Benefits on visual acuity and cognitive development have been largely established in term[8,9] and preterm[10,11] infants fed ω-3 LCPUFAs-supplemented formula.[12]

Typically, shellfish contain substantial quantities of digestible proteins, essential amino acids, bioactive peptides, ω-3 LCPUFAs, astaxanthin and other carotenoids, vitamin B_{12} and other vitamins, minerals, including copper, zinc, inorganic phosphate, sodium, potassium, selenium, iodine, and other nutrients, which offer a variety of health benefits to the consumer.[13,14] Seafood is low in calories compared with other animal foods. For example, a 100 g serving of shrimp provides approximately 106 kcal of energy, whereas the same amount of fish provides 110–150 kcal, lean beef 250 kcal, and roasted chicken 200 kcal of energy.[15]

Seaweed has been part of the human diet, especially in Asia, for centuries and has gained popularity in western countries.[16,17] Seaweeds are extensively utilized in the food industry and are becoming increasingly commercially available because of their properties as food additives,[18] their nutritional values,[18,19] and implied medical applications.[19,20] Seaweed intake has been linked with reduced risk of breast and colorectal cancers, perhaps owing to the extraordinary fiber and vitamin content.[21] Both kelp and laver contain a large amount of iodine, a vital element for thyroid health.[17] Laver is an excellent source of vitamins A and C, while kelp is a good source of folic acid.[17] Human exposure to arsenosugars (AsSugars) is fairly high in Asia owing to a diet rich in seaweed.[22] Fortunately, there are no indication for acute and chronic toxicity related to seaweed ingestion from epidemio-logical studies.[21]

According to the State of World Fisheries and Aquaculture, published by the United Nation’s Food and Agriculture Organization (FAO), in 2014, an amount of 167.2 million metric tons (MMT) of seafood was globally available, with landings of shrimp, American lobsters, and cephalopods at 3.5, 0.16, and 4.3 MMT, respectively.[23] Total fish production in 2016 reached an all-time high of 171 MMT, of which 88% was utilized for direct human consumption with per capita consumption of 20.3 kg and an export value of U.S. $143 billion.[24] An estimated 38% of the 23.8 MMT of seaweeds in the 2012 global harvest was eaten by humans.[25] The global harvest of seaweeds in 2013 was estimated at U.S. $6.7 billion.[26]

Consumer demand for shellfish and other seafood has resulted in a significant rise in their wild catch and aquaculture in fresh, brackish, and marine waters, with a total production of 73.8 MMT in 2014, at an estimated value of U.S. $160 billion. This included 16.1 MMT of mollusks composed of 104 species valued at U.S. $19 billion and 6.9 MMT of crustacean valued at U.S. $36.2 billion.[23] Aquaculture is projected to grow at almost 39% annually, with an estimated production of about 102 MMT in 2025.[23] Shellfish formed 38% of total seafood traded in 2013, with shrimp being the most popular shellfish.[27]

In the United States, where the per capita shrimp consumption of about 1.73 kg was recorded in 2012, almost 90% of the shrimp consumed came from imports.[28] The per capita shellfish consumption in 2013 was 4.9 kg, subdivided into 1.8 kg of crustaceans, 0.5 kg of cephalopods, and 2.6 kg of other mollusks.[23] In 2014, an amount of 146.3 MMT of seafood was used as human food, giving a global per capita seafood consumption of 20.1 kg and contributing to about 20% of total average per capita intake of animal protein.[13] Per capita seafood consumptions of 25.8 and 35 kg were also reported in 2017 in the European Union (E.U.) and southern Europe, respectively.[13]

Evidently, seafood is a highly consumed and traded commodity, and therefore, intentional or unintentional contamination with toxic elements like arsenic may become technical barriers to trade. For example, in December 2013 China imposed a ban on all U.S. imports of geoduck clams (*Panacea generosa*), a large edible saltwater clam found along the Pacific Northwest extending from northern California to southeastern Alaska, citing high levels of arsenic contamination. Revenue from U.S. exports of geoduck clams are upward of $80 million annually with about 90% of all exports going to China.[29]

Jennings et al. acknowledged the need for seafood supply to not only meet the needs and preferences of consumers but also for it to be sustainable and provide nutritional benefits while posing minimal health risks.[30] Despite the many health benefits of seafood, they are unfortunately inherently contaminated with arsenic, especially organic arsenic species.[31] It is therefore critical from a risk-based approach to conduct arsenic speciation analysis in order to determine the arsenic species present and their relative proportions consumed by humans and thus enable more accurate risk assessment.[32–34]

Seafood is the major dietary source of total arsenic in humans,[35] excluding regions with widespread elevated drinking water contamination.[36–39] Organic arsenic predominates in seafood; however, this is not always the case, as there are reported cases of elevated inorganic arsenic levels in seafood such as in edible seaweed *Hijiki* (60–150 $\mu g\ g^{-1}$, iAs),[40] fish from Thailand,[41] and mussel from Norway.[42] Marine algae and shellfish are the seafood exposure sources with the greatest diversity of arsenicals.[43] Among these arsenicals the potential for biotransformation upon ingestion varies considerably.[44] Arsenic speciation (Figure 1) is complicated, and diverse arsenic species display great difference in toxicities.[45]

The chemical state of arsenic influences its bioavailability, mobility, and toxicity, among other properties.[46] Arsenic exists in four oxidation states in the inorganic form as trivalent arsenite (iAs^{III}) and thermodynamically stable pentavalent arsenate (iAs^{V}).[47] Elemental arsenic (As^{0}) and arsine, H_3As (As^{-III}), exist in strongly reducing conditions.[48–50] Arsenic

exists in organic form where arsenic is bonded to carbon as low molecular weight compounds like monomethylarsonate (MMA), dimethylarsenate (DMA), arsenobetaine (AsB), arsenocholine (AsC), trimethylarsine oxide (TMAO), and tetramethylarsonium ion (TETRA); high molecular weight arsenosugars (AsSugar) and arsenolipids (AsLipids); and in complexed form as arsenopeptides (glutathione (As-GSH), and phytochelatins (AsPC)).[46,51,52]

Arsenobetaine (AsB) is the main arsenical in seafood, commonly comprising in excess of 90% of the total arsenic in fish.[53–56] AsB is the major polar arsenical, which together with AsSugars and a range of other lipophilic arsenicals account for over 70 naturally occurring organoarsenicals found in seafood.[34,37] There is great diversity in the level of arsenic in seafood, but arsenic in most samples falls within the mass fraction range of about 5 to 100 $\mu g\ g^{-1}$ dry mass.[34] Sirot et al. reported the levels of inorganic arsenic (iAs) in 30 fish species collected in France as 0.005–0.073 $\mu g\ g^{-1}$ on wet mass basis. This clearly demonstrated that the proportion of iAs to total arsenic content, mostly AsB, was 100-fold lower.[57]

The aim of this paper is to give a comprehensive summary of the current state of understanding of the various aspects of organoarsenical formation in the marine food chain in terms of occurrence, exposure, metabolic transformation, and toxicity of smaller-molecule oxo-arsenicals, arsenosugars, arsenolipids, and thio-arsenicals. A brief discussion about the mechanism of toxicity of inorganic arsenic is also presented in the paper because it is the arsenic species with well-understood adverse effects. This may seem out of place but is important for the understanding of the general behavior of organoarsenicals. Where the term arsenic is used, it means inorganic arsenic (iAs).

2. METABOLIC TRANSFORMATION AND TOXICITY OF ARSENIC

An enormous assortment of biologically relevant arsenic species has been characterized in samples of dietary sources.[16,34,55,58–60] Arsenic toxicity, bioaccumulation, and mobility are greatly dependent on the chemical state in which the element appears and the extent of methylation through the metabolism process.[38,43,61,62] iAs^{V} and iAs^{III} are categorized as nonthreshold Class I carcinogens,[63] with acute toxicity of LD_{50} = 15–42 mg/kg body mass, while simple methylated arsenicals are deemed to pose intermediary toxicity (LD_{50} = 890–10600 mg/kg body weight), and the tetraalkylated compound AsB, present in fish and the principal dietary source of arsenic exposure for humans, is nontoxic with LD_{50} = >10000 mg/kg body weight and is primarily eliminated intact by humans in the urine.[56,64]

Typically the lower the oxidation number is, the higher the toxicity is, and the higher the methylation is, the lower the toxicity is, thus producing the following order of toxicity for arsenic species in human cell lines: monomethylarsonous acid (MMA^{III}) > dimethylarsinous acid (DMA^{III}) > arsenite (As^{III}) > arsenate (As^{V}) > trimethylarsine (TMA^{+}) > dimethylarsinic acid (DMA^{V}) = monomethylarsonic acid (MMA^{V}) > trimethylarsine oxide (TMAO) > arsenocholine (AsC) > arsenobetaine (AsB).[65–68] Moreover, AsB, AsC, TMAO, AsSugars, AsLipids, and other organoarsenicals are usually mildly toxic compared to iAs species.[34,45,69]

Due to the extreme toxicity of iAs, microalgae and other living organisms may undergo dissimilar processes to lessen the toxic effects, including cell surface adsorption, arsenite oxidation and arsenate reduction,[70,71] methylation,[72] conversion to AsSugars or AsLipids,[73] chelation of iAs^{III} with glutathione and phytochelatins,[74,75] and elimination from cells.[45] Arsenic detoxification occurs through a series of biotransformations in biotic systems which produce a wide range of organoarsenicals, whereby arsenic is covalently bonded with one or more carbon atoms containing functional groups.[75,76] Toxicity is instituted once liver methylation ability is impeded or surpassed.[77–79]

It is important to note that discussions on arsenic toxicity are mainly in reference to inorganic arsenic and methylated arsenicals (MMA and DMA) since their toxicity mechanism is well established and understood unlike for AsSugars and AsLipids which are yet to be fully elucidated. Organoarsenicals have not demonstrated acute toxicity; therefore, their toxicity may arise from metabolic transformations that lead to formation of highly toxic metabolites.[52,58,64] For example, the toxicity of AsSugar and AsLipids may arise from their metabolic breakdown to other arsenicals such as DMA^{V}, which is also the metabolite of iAs found in urine and is a known tumor promoter and confirmed carcinogen in experimental animals.[80,81]

Liver, kidneys, heart, and lungs are main repository organs of arsenic, with slight buildup in brain and muscle tissues.[62] This buildup is linked with a variety of ailments including diabetes, hepatotoxicity, cancer, and nephrotoxicity. Arsenic can cause thiamine deficiency by lowering its accessibility, leading to lactic acidosis by enhancing lactic acid concentration.[62] In addition, arsenic may cause genotoxicity by impeding DNA repair mechanism and further stimulates oxidative stress by producing reactive nitrogen species (RNS) and reactive oxygen species (ROS).[62,82,83]

In biological systems, arsenate can replace phosphate and form esters that resemble phosphate esters, which are abundant in biomolecules, from the sugar phosphates of intermediary metabolism, to membrane phospholipids, to the phosphate backbone of genetic materials like deoxyribonucleic acid (DNA) and ribonucleic acid (RNA).[84] However, these compounds are less stable because they are more delicate than the subsequent phosphate esters, which is partly attributed to the bond lengths and bond angles.[85] The P-O bond length in phosphates is almost 1.5 Å, whereas the bond length of As-O in arsenates is roughly 1.6 Å to 2.0 Å. Arsenic usually form lengthier bonds than phosphorus (Figure 2).[85] In addition, arsenic angles are considerably less obtuse than the phosphorus angles,[84] i.e., the O-P-O bond angle is about 117°, whereas the O-As-O bond angle is roughly 100°, with minor variabilities in diverse compounds. Therefore, since longer bonds are fragile, arsenate esters disintegrate more easily than phosphate esters.

Within the cell, metabolic enzymes which utilize phosphate may also incorporate arsenate in alkylation, acylation, or phosphorylation reactions because of their isosteric and isoelectronic nature.[86] For example, arsenate inhibits the formation of ATP as a result of generation of delicate anhydrides and also uncouples ATP synthesis during oxidative phosphorylation by coupling with adenosine diphosphate (ADP) in the presence of succinate in the mitochondria to form ADP-arsenate rather than ATP.[87–89] This disrupts phosphorus

metabolism since ADP-arsenate may be utilized as a substrate for hexokinase, which under normal conditions produces glucose-6-phosphate, the first intermediary in the glycolytic pathway.[87] This inhibits hexokinase by negative feedback. The glucose-6-arsenate produced by hexokinase is then transformed to glucose-1-arsenate by phosphoglucomutase, proving that intermediary metabolism can produce arsenicals.[86] The rate constant for spontaneous breakdown of glucose-6-arsenate has been shown to be 4×10^{-4} s^{-1}, compared to 4×10^{-9} s^{-1} for glucose-6-phosphate. Therefore, the short half-life of arsenate ester causes it to spontaneously hydrolyze 10^5 times faster than the phosphate ester, which is the major cause of decoupling action of arsenate in oxidative phosphorylation,[87] and therefore cells essentially starve for scarcity of metabolic intermediates.[45,75,84,86,90]

The other factor that potentially contributes to the instability of arsenicals is the fact that iAs^V is swiftly reduced to iAs^{III} within the cells.[84] The biological half-life of As is roughly 4 days, which is dependent on the manner of exposure as iAs^{III} is considered to have a shorter half-life in comparison to iAs^V.[91] iAs^{III} is the most hazardous and toxic form of inorganic arsenic, which block sulfhydryl (−SH) groups by creating robust bonds of metallic nature with thiols in proteins and small molecules.[84] iAs^{III} toxicity is due to its high affinity for thiol groups, causing allosteric inhibition of respiration by binding to vicinal thiols in pyruvate dehydrogenase (PDH) and 2-oxoglutarate dehydrogenase,[90] with resultant membrane destruction and cell death by generating reactive oxygen species (ROS).[45,92] The allosteric inhibition of PDH, a vital precursor of acetyl-CoA, not only restricts the generation of ATP in the electron transport chain but also impedes the formation of gluconeogenesis intermediaries.[93–96] Moreover, research findings indicate that arsenite is able to traverse across the blood-brain barrier.[97–99]

Due to scarcity of toxicity and long-term exposure data for organoarsenicals in humans or other mammals, health hazards from exposure to organoarsenicals are challenging to evaluate. Most of the injurious effects of inorganic arsenic have been documented, but the uncertainty concerning the threat to the people exposed to organic arsenic, especially from seafood, and the dosage needed to trigger these effects still linger. Numerous investigations have contemplated the latent carcinogenicity from the formation of the metabolite DMA^V,[100–104] centered on elevated dose exposure studies in rats to DMA in water[81] or diet.[105] There is, however, compelling indication that the rat model is invalid for human exposure to DMA, because of the difference in the metabolic pathways of rats and humans and also because these studies are not capable of evaluating the pathway to DMA (from iAs or orgAs compounds) and the intermediary effects.[106]

On the basis of projected exposure level and expected metabolism, it seems unlikely that arsenic in seafood can significantly promote arsenic-associated carcinogenic effects.[100] The bulk of arsenic in seafood exist as AsB, which is benign and is rapidly excreted from the body intact. Amounts of TETRA resulting from dry cooking or AsB-containing fish are unlikely to reach toxic levels. In addition, levels of iAs and methylarsenicals in seafood are relatively low to allay suspicions of their potential detrimental effects in seafood consumers.[100,107]

Whereas no deductions can be made regarding the effects of organoarsenicals, proof of toxicity from AsLipids and organoarsenic metabolic intermediates from in vitro assessment confirms the necessity for animal and human research to assess probable health impact of arsenic in seafood.[108,109] The majority of research on natural AsLipids has focused on the polar lipids, leading to the characterization of arsenic-containing fatty acids (AsFAs) and arsenic-containing hydrocarbons (AsHCs). Profound discernment of arsenic biochemistry may perhaps be garnered from characterization of the additional lipid fractions.[110]

2.1. Methylated Arsenicals.

Methylarsenicals are present in marine food as MMA and DMA at low levels. Other methylated arsenicals include TMAO, AsB, AsC, and TETRA. Methylarsenicals in marine ecosystem are generated by phytoplankton, bacteria, and microbial breakdown of botanical matter from iAs and are introduced into the seafood food chain.[70,111] Phytoplankton absorb iAs^V in the euphotic surface waters and successively transform it to DMA and MMA.[112–116] Anaerobic members of archaea and bacteria are known to biotransform iAs into both volatile (methylarsines) and nonvolatile (MMA and DMA) species.[117–120]

Three metabolic pathways have been proposed for arsenic biotransformation.[112,121–123]iAs undergoes enzymatically biotransformation into several methylated metabolites following the classical Challenger's metabolic pathway as follows: $[iAs^V] \rightarrow [iAs^{III}] \rightarrow [MMA^V] \rightarrow [MMA^{III}] \rightarrow [DMA^V]$.[121,122,124–126] DMA^V can be reduced to DMA^{III} and further methylated to trimethylarsine (TMA^{III}) via TMAO intermediate.[127] Mammalian systems do not subsequently produce arsines except under extraordinary conditions.[128,129]

The Challenger pathway illustrates the reduction of pentavalent iAs^V and MMA^V to their trivalent species, iAs^{III} and MMA^{III}, followed by an oxidative methylation phase where S-adenosylmethionine (SAM) acts as the methyl donor, producing MMA^V and DMA^V as major metabolites. Although the precise pathway in humans has never been entirely understood,[62,130] it has for long been deemed as a detoxification process.[131–133] Biotransformation on iAs results in the production of MMA^{III} and DMA^{III},[134,135] which are more toxic than iAs, and therefore, biotransformation of iAs should be generalized as a detoxification process in micro-organisms.[93] The Challenger pathway is coherent with the distribution of arsenicals in urine and can be entirely verified using $(CH_3)_3S^+$ as a CH_3^+ donor and SO_2 as the reducing agent in likeness with the Meyer reaction, which is an uncatalyzed oxidative addition reaction employed in the preparation of MMA^V from iAs^{III} and methyl halide.[91,121,126,127]

Other pathways proposing glutathione- or protein-conjugated intermediaries have been advanced by Hayakawa et al.[126] in 2005 and Naranmandura et al.[125] in 2006, respectively, though their chemical basis is questionable because they involve accepting CH_3^- group.[136] They, however, appear to be in agreement with the belief that trivalent arsenicals were confirmed to be readily absorbed by the organs/tissue and linked to cellular proteins, as a substitute to elimination.[137] The two pathways propose that DMA^V and MMA^V ought to be final products (instead of intermediaries) of arsenic biotransformation,[138] because trivalent arsenic, whether in glutathione or protein complex states, is subjected to reductive methylation without being oxidized.[91] MMA^{III} that has long been considered as an

transitory intermediate in the methylation pathway is rather a stable metabolite of iAs and has been detected in appreciable (e.g., effect levels) concentrations in hamster liver, rat bile, and human urine following exposure to iAs.[127,139]

Production of methylarsenicals is linked to the growth phase or phytoplankton nutritional state.[112] Production of DMA^V increases gradually, while DMA^{III} and MMA^{III} remain fairly constant during the lag phase of phytoplankton growth. Formation of DMA^V is elevated when the proportion of phosphate-to-arsenate declines implying enhancement of production at phosphate-replete conditions.[112,140]

MMA and DMA are generally available in trace amounts or are not present in seafood.[100] Measurable amounts have mainly been detected in fatty types of fish.[141] Extremely low amounts (i.e., μg As/kg) of DMA have been detected in mackerel and herring and in prawns but were not measurable in cod, dab, haddock, sole, plaice, tuna, or whiting.[100,141–143] DMA has also been detected in seaweed like kelp.

The International Agency for Research on Cancer (IARC) classification of the carcinogenicity of arsenic species categorizes MMA and DMA as Group 2B (possible carcinogen to humans).[63] In vivo studies have demonstrated that methylated arsenic metabolites can traverse the placental barrier, although the methylation capacity is enhanced during gestation as a protective measure for the developing fetus.[134]

It has been suggested that MMA^{III} is more hazardous and toxic than iAs to the liver, skin, and lung cells.[144] In addition, DMA^{III} is more toxic than DMA^V and iAs[145] because DMA^{III} has neutral charge and can readily permeate cells (up to 16%), but DMA^V which has a negative charge can scarcely enter cells (0% to 2%).[146] The methylated trivalent arsenicals, MMA^{III} and DMA^{III}, have higher cytotoxicity than As^{III} and As^V, which are more cytotoxic than the methylated pentavalent arsenicals, MMA^V and DMA^V.[91] The adverse effects of arsenic are therefore intimately connected to its metabolism and is significantly reliant on the methylation level and the valence state of the metabolites.[147]

2.2. Trimethylarsine Oxide (TMAO).

TMAO has been isolated in various species of aquatic organisms as a minor arsenic species, seldom identified except in miniscule amounts.[51,148] Quantities are much lower in stored, frozen fish than in fresh fish, likely due to post-mortem degradation, but dietary ingestion of TMAO is most likely small.[51,100,149] TMAO is fundamentally benign, with an acute oral LD_{50} for arsenic in mice of 5500 mg/kg.[100,150]

2.3. Arsenocholine (AsC).

Arsenocholine is a metabolic predecessor for AsB in aquatic animals.[100,151,148] After inoculation of labeled AsC, it is swiftly taken up and converted to AsB with minimum breakdown to iAs, MMA, or DMA.[100,151,152] Even though findings on AsC toxicity are scanty, it is deemed to be benign.[100] The acute oral LD_{50} for arsenocholine in mice was 6500 mg/kg, whereas the acute intravenous LD_{50} was 187 mg/kg.[100,152]

2.4. Arsenobetaine (AsB).

Seawater contains traces of arsenic (~2 μg/L), which is bioaccumulated by aquatic organisms by up to 5 orders of magnitude.[51] The bulk of arsenic in aquatic organisms exist as AsB, mainly found in fish and shrimp, and as AsSugars, mainly found in marine algae.[21] AsB is an arsenic analogue of the amino acid derivative, glycine betaine, and it is extremely stable to hydrolysis or metabolism.[43] The source of AsB in the food web is vague, though various speculations concerning its biosynthetic pathway have been proposed.[153,154] Arsenic, in AsB, is oxidized with four stable carbon bonds which are enzymatically or thermally recalcitrant. Even though AsB can be degraded by microflora existing in human gut, their incubation time (7 days)[155] is lengthier than practical gut retention, and this metabolic pathway has not been witnessed in vivo; thus, AsB is usually not converted in humans and other mammals.[43,51,100]

This makes AsB biochemically quasi-inert, which may explain why this species, though readily accessible, does not convert into other metabolites when consumed by humans and is swiftly eliminated from the mammalian body intact.[54] The postulation that the four stable As-C bonds account for the innocuous nature of AsB earns credence from the fact that tetramethylarsonium ion (TETRA) and arsenocholine (AsC), both of which are structurally analogous to AsB, also display no indication of toxicity (Table 1, Figure 1).[54,69] AsB is nonmutagenic and does not show cytotoxicity, immunotoxicity, or biotransformation in mammalian cells. The acute oral LD_{50} of AsB in mice is more than 10000 mg As/kg.[64]

There is adequate proof that higher aquatic animals do not produce AsB, but the complete description of its formation remains unclear.[148] Experimentally, AsB has been proven to be efficiently assimilated from seawater by mussels, whereas shrimp and fish accumulate AsB efficiently only from food, which includes phytoplankton, among others.[156,157] In mussels, retention of AsB is dependent on the salt content of their ambient water, which supports the notion that AsB can mimic an osmolyte.[43] Likewise, the tendency to increase total arsenic with salinity was witnessed among three species of pelagic fish, where AsB is presumed to be the main arsenic species, also implying AsB absorption and retention is linked to salinity.[43,157] This experiment gains credence from data that show a positive correlation between arsenic content and salinity of mussels kept in aquatic environment of changing salinities.[156]

2.5. Tetramethyl Arsonium Ion (TETRA).

TETRA is a minor arsenical in finfish but the main species in various mollusks.[51,148,161] Amounts ranging from 0.2 to 16 μg/g were reported in different organs of a few clams.[148] Concentrations of TETRA can be enriched by freezing or dry cooking (grilling, roasting, and baking) at temperatures above 160 °C, particularly in burnt meat, possibly owing to thermal decarboxylation of AsB.[162] Consequently, TETRA concentrations above 1.0 μg/g dry mass have been documented in cooked fish where TETRA was not present before cooking.[100] The halogenated TETRA has substantial acute toxicity; in mice, the acute oral LD_{50} of TETRA-chloride was 890 μg/g. Conversely, such toxicity may arise from the halogen anion and not TETRA as analyses of synthetic TETRA-hydroxide have revealed nontoxicity.[160] Because of the reduced amounts of TETRA in ingested fish, acute toxicity by

TETRA is improbable; the highest documented amounts in grilled or roasted fish are 0.571 μg/g wet basis and 1.79 μg/g dry basis.[100,162,163]

2.6. Thioarsenicals.

Thio-arsenicals and oxo-arsenicals are structurally similar with sulfur replacing oxygen and are produced when oxo-arsenicals are exposed to hydrogen sulfide (H_2S).[164] Knowledge of thio-organoarsenicals is fairly recent, and few studies have examined their production processes and detection techniques.[165] The main focus of arsenic speciation has been on oxo-arsenicals, owing to their abundance in nature.[166] Speciation analysis of thio-arsenicals is a challenging task, and there is need to exercise caution during sample storage, pretreatment, extraction, separation of arsenic species, and detection.[91]

Despite the latest advances in characterization and detection of thioarsenicals, there are lingering intricacies in their analysis in biological matrices, especially seafood and seaweed, owing to the complexity of arsenic metabolism, the homophyly of oxo-arsenicals and thio-arsenicals,[166] and lack of standards for thio-arsenicals.[91] Many thio-arsenical standards must be produced in specific laboratories, and in certain instances, the production is grueling owing to the instability of species, like $DMMTA^{III}$.[91] Figure 3 enumerates the names, abbreviations, and chemical structures of the main trivalent and pentavalent arsenicals involved in arsenic metabolism.[91]

Presence of dimethylmonothioarsinic acid ($DMMTA^{V}$) and dimethyldithioarsinic acid ($DMDTA^{V}$) in human and animal urine, which may cause interferences with metabolic processes, after ingestion of AsSugars has led to the recent upsurge in the research on thio-arsenic species.[165,166] Methylated thio-arsenicals have been identified in urine samples following long-term ingestion of iAs-contaminated drinking water or intake of AsSugars.[133] Following intake of AsSugars, $DMMTA^{V}$ appeared at trace levels in the urine of Japanese males.[167,168] In sheep consuming algae with elevated AsSugars content, 2-dimethylarsinothioyl acetic acid (thio-DMAA) was identified in urine.[166] Trace amounts of thio-DMAA and thio-DMAE were detected in the serum following intake of an oxo-AsSugar.[169] Wang et al. reported the presence of thio-DMAA in human saliva samples following ingestion of Chinese seaweed, with the usual excretion profile observed in urine.[170]

The toxicological significance of thio-arsenicals to organisms is still uncertain, but there are indications that methylated thio-arsenicals have appreciable toxicity compared to their oxo-anion counterparts.[171] As regards human epidermoid carcinoma, $DMMTA^{V}$ has higher cytotoxicity than DMA^{V} (LD_{50} = 10.7 and 843 μmol/L, respectively).[172] $DMDTA^{V}$ has injurious consequences in culture cells that result in DNA impairment.[173] Thio-DMA^{V} has been observed as a product of both iAs[133] and AsSugar metabolism.[168,169] Considerable toxicity from thio-DMA^{V} has been witnessed in skin, bladder, liver, and lung cells, which is partly linked to its extreme cellular bioavailability.[174–179] Thio-DMA^{V} has been proven to generate ROS in healthy cells[174–176] and to disturb cellular stress response, even at picomolar levels, in oxidatively stressed cells.[101–103] Thio-DMA^{V} exhibited no genotoxic mode of action in lung cells,[177] but DNA injury and alterations in gene expression were

witnessed in bladder cells exposed to such species.[176] Epigenetic effects from long-term exposure to thio-DMA^V have also been detected at low picomolar levels.[180]

2.7. Arsenosugars (AsSugars).

AsSugars is a general expression that jointly denotes ribofuranosides containing arsenic.[21] There are at least 20 known AsSugars in different molecular forms, of which four (AsSugars-OH, PO_4, SO_3, and SO_4) are the most commonly occurring in aquatic systems.[21,43,54,100] Arsenosugars are the predominant arsenicals present in macroalgae[159,181–193] and have also been reported in clam,[194,195] gastropods,[196] shrimp,[197] mollusks,[198] and oyster tissue.[199]

Most AsSugars contain a dimethylarsinoyl group, where arsenic is pentavalent and connects to two methyl moieties, at C5 of the ribose ring and to oxygen, with a variety of substituents at the C1 position of the sugar backbone shown in Figure 4. The dimethylarsinoyl moiety of the oxo-AsSugars is prone to be protonated at low pH (below 3), thus bestowing a cationic and polar nature to the molecule. However, this property is countered by the aglycone moiety if it holds an acidic moiety because the acid-base characteristics witnessed are essentially regulated by the aglycone.[16] With the exception of AsSugar-glycerol, the other oxo-AsSugars with widespread occurrence possess a strongly acidic group. The acidic potency intensifies from the phosphoric acid ester, followed by the sulfuric acid ester through to the sulfonic acid ester.[200,201]

AsSugars may occur as thio-AsSugar where the oxygen is replaced by sulfur and as trimethylarsonium compounds, as shown in Figure 4.[21,54] Naturally, corresponding oxo and thio analogues are present, though the pentavalent dimethylated oxo species predominate.[16] Most AsSugars are polar. There are several other lipophilic arsenic-containing oxo-ribofuranoside. The molecular structure of the first arsenosugar phospholipid (AsPL) identified by Morita et al. in 1988 is shown in Figure 5.[183] Garćia-Salgado et al. identified additional AsPLs from two species of brown macroalgae in 2012.[184]

The polarity of AsSugars, which is based on their behavior in reversed-phase (RP) chromatography, shows that oxo-AsSugars are more polar than their thio analogues, with the AsSugar-glycerol being the species with the highest polarity.[16,168] The presence of diastereomeric sulfonate and carboxylate oxo-AsSugar species in natural samples was revealed following NMR studies.[16,19]

AsSugars are substantially more chemically labile than AsB, and biodegradation is probable when they are exposed to an acid or base hydrolysis or modeled gastric-type environment.[202–204] However, degradation of AsSugars is not entirely stimulated by the chemical conditions and may be initiated by enzymatic and/or microbial activity.[205] Only limited information is available with regards to temperature stability of AsSugars which are neither decomposed by cooking of seaweed nor by stomach acid digestion, which suggests that the occurrence of DMA^V after AsSugars ingestion is attributable to either enzymatic or microbial activity in the human body.[202,206] Oxo-AsSugars stability persisted during transitory heating to 100 °C for 10 min even though this does not demonstrate normal cooking conditions. At elevated temperatures and under acidic conditions, some AsSugars

undergo acid hydrolysis to yield the disintegration product AsSugar 254 (DMAsSugarHydroxy) shown in Figure 6.[205]

Not much is known concerning the source or potential function of AsSugars in biological systems, though it is assumed to be produced in organisms because of detoxification and excretion after ingestion of iAs^V naturally occurring in seawater.[207,208] Probable pathways for their formation and conversion have been illustrated in literature.[21,207,209] AsSugars are not just the major arsenicals in seaweed but also exist in an enormous quantity in filter feeding herbivorous mollusks and gastropods from consuming algae or phytoplankton.[16,43,100,210] The focus of research has been on the characterization and quantitation of AsSugars present in diverse aquatic macroalgae, regularly referred to as seaweed or kelp, and commercially accessible algae products, whose intake is promoted for their health benefits but may be a cause of exposure to arsenic that is intrinsically present in them.[16,211,212] Aquatic organisms have higher levels of AsSugars compared to the freshwater and terrestrial organisms where the top-most detected amounts in sea algae and commercial kelp powders were 10–40 μg As/g (dry weight).[18]

In cells of mammals, generated AsSugar was not cytotoxic at micromolar levels.[36] Of the four AsSugars with widespread occurrence in seaweed, only two (AsSugar-OH[101,102,21,213] and AsSugar-SO_3 [101–103]) have been assessed and demonstrated significantly reduced cytotoxicity in comparison to iAs. However, a trivalent derivative of AsSugar-OH (DMA^{III}-AsSugar-OH) displayed substantial toxicity to the cell, but this arsenic species has at no time been witnessed in biological systems.[21] DMA^V-AsSugar-OH has been assessed with cell cultures and presented no cytotoxicity at the micromolar level, indicating that the AsSugars in their native state in dietary sources have extremely decreased toxicity and are likened to AsB, though this conclusion was made upon the evaluation of a single AsSugar.[54]

AsSugars that were previously reported in literature as not exhibiting cytotoxic or mutagenic activities[187] have demonstrated bioaccessibility following metabolism within the human body.[202] The high intake of AsSugar and the resemblance they share with iAs with regards to metabolism and accumulation suggest that AsSugar may display more toxicity than earlier assumed.[21] For example, trivalent AsSugar is more cytotoxic (IC_{50} = 200 μmol/L, 48 h exposure) than the corresponding pentavalent species (IC_{50} > 6000 μmol/L, 48 h exposure) in typical human epidermal keratinocytes. AsSugar metabolites may also occur in trivalent forms, which have thus far not been identified in biota, likely as a result of their reactivity, but have demonstrated elevated cytotoxicity while directly linked to plasmid DNA at the μmolar level.[21] Reduction of DMA^V-AsSugars is envisaged to happen promptly in vivo via reaction with thiol compounds, thus making these AsSugars hazardous to human health.[21,214,215]

AsSugars are metabolized and biodegraded to various minor compounds after retention in the body.[202] Assimilation and elimination of AsSugars[167,202,210] is much slower than AsB or AsLipids[216,217] and is highly variable between individuals.[202] Volunteers from single consumption studies of seaweed showed either no buildup or just a slight elevation in urinary arsenic content, while others eliminated up to 95% of the consumed arsenic.,[167,169,202,203,210,218] The same consumption experiment was repeated with volunteers who

showed the least (4%) and the most (95%) recovery of the consumed AsSugars, and consistent outcomes were reported.[169] Difference in metabolism by gut microflora, permeation past intestinal barriers, and conversion within the liver may provide explanations for the retention variabilities between individuals.[43,219]

DMA^V is the main metabolite for AsSugar in human urine, although the transformation sites are yet to be confirmed.[21] Feldmann et al. studied sheep, which perennially fed on seaweed and therefore were chronically exposed to AsSugars, to provide further insight into the metabolism of AsSugars because of their metabolic similarity with humans.[214] Elevated urinary arsenic concentration peaked about 20 h after ingestion and were reported in all 12 sheep in the study.[215] However, tissue arsenic concentrations were not significantly elevated, [214] and only 4–20% of consumed arsenic was detected in feces, indicating that most arsenic was eliminated via urine.[215] Assuming that this interpretation is accurate, the results could not be verified due to challenges in acquiring 24 h urine samples from the sheep.[215] Unfortunately, sheep that were used as proxies to study human susceptibility to cancer risks have a limited lifespan of four to six years, which is not sufficient to assess the long-term exposure effects. However, the sheep study underscores the need for thorough investigation of foodstuff that contains arsenic in a state that is metabolized, but whose toxicological latency is unknown.[54]

2.8. Arsenolipids (AsLipids).

Human exposure to AsLipids arises from ingestion of seafood for example fatty fish,[56] algae,[184,220] and crustaceans.[51,221] However, there is scarce knowledge with regard to abundance, identity, and toxicity of these compounds.[56,222] AsLipids are an emerging species of interest that have relatively high natural levels in marine animals and algae.[223] In seafood, AsLipids comprise up to 70% of the total arsenic content,[224] with amounts between 0.3–3.6 mg As/kg dry weight.[225] The greatest quantities are obtained in fatty fish like herring and mackerels.[56] AsLipids are believed to move upward in the food chain, starting with algae to higher organisms such as fish, with the possibility of endogenous production in the organism since the detected arsenic-containing fatty acids (AsFAs) show similarities to common fatty acids found in aquatic organisms.[56,108] Arsenic-containing hydrocarbons (AsHCs) are present in various aquatic systems, such as herring,[225] tuna,[226] cod,[227] fish oils, [224,228,229] and edible brown algae.[220,223,230]

AsLipids occur as derivatives of fatty acids (AsFAs),[37,110,220,225,228,229,231–237] hydrocarbons (AsHC),[37,110,220,225,228,229,231,233–238] phosphatidylethanolamine (AsPE), [239,240] phosphatidylcholine (AsPC),[239–241] fatty alcohols,[231] and AsSugar-PLs.[184,220] The existence of arsenic in lipid extracts of fish and algae was originally documented by Lunde in 1968,[242] but their structures remained unknown.[234] Several molecular structures of AsLipids have been elucidated based on their exact mass and their product ion mass spectra, demonstrating the chemical complexity of these compounds in seafood.[37,184,220,232,235] Subsequent biochemical studies showed that AsLipids in unicellular algae involved three main lipid types,[243] and similar species were also detected in clam tissues resulting from algal-clam symbiosis.[234,244]

Morita and Shibata in 1988 successfully purified and determined the structure of the main AsLipids in the brown macroalga, Wakame (*Undaria pinnatifida*), which was found to be a phospholipid with an AsSugar headgroup (Figure 4).[183] Garcia-Salgado et al.[184] and Raab et al.[220] were able to extract AsPLs and other arsenicals from brown macroalgae species. AsLipids were first detected and identified in fish oils in 2008, where arsenic was directly linked to either a long chain fatty acid[232] or a hydrocarbon[224] (Figure 7). Characterization of AsLipids is work in progress with more than 50 known AsLipids.[43]

AsLipids primarily elicited research interest due to their novel structures, their likely role in membrane biochemistry, and since they exist in ordinary seafood with potential health concerns based on arsenic toxicity.[34] Advances in the biochemistry and toxicology of AsLipids has been impeded by the difficulty related to separation and analysis of AsLipids, [245] trace amounts of AsLipids in marine samples compared to polar arsenicals,[56] limited knowledge on the stability of the analytes in the course of ordinary sample preparation steps, [246] and absence of standards and quantitative analytical methods.[223]

The identification and quantification of AsLipids has been made possible by concurrent analysis using LC-ICP-MS for element specific detection and ESI-MS for structural determination.[233–238] Several AsHCs and AsFAs have been synthesized for confirmation of identity.[234,247–249] However, there are still no standards or reference materials accessible for AsLipids and AsSugar phospholipids (AsSugar-PLs). For example, standards for unsaturated AsLipids are not available, which incidentally are difficult to synthesize and therefore must be isolated from fish muscle.[225]

Lack of standards is a progressive challenge because as more compounds get identified there is a higher demand for new standards. Pure compounds are necessary for accurate quantification and to aid in the investigation of their metabolic transformation and potential toxicities.[46] Improved knowledge with regards to chemical structures, amounts, bioavailability, and toxicity of the specific AsLipids is necessary for a more comprehensive risk assessment of arsenicals found in food and feed.[43]

AsLipids are of toxicological concern because their metabolites are similar to iAs^{III} a well-characterized carcinogen.[217,222] However, the molecular modes of action regarding their toxicity as well as their metabolism in liver remain unclear.[250] AsHC 332, AsHC 360, and AsHC 444 have recently shown substantial toxicity in various in vitro and in vivo systems.[61] In an in vitro blood-brain barrier model, it was shown that AsHC 360 [1-(dimethylarsinyl)heptadecane] was up to 5-fold more cytotoxic than iAs^{III}, followed by AsHC 332 [1-(dimethylarsinyl)pentadecane)] and AsHC 444 [1-(dimethylarsinyl)tricosane], which were 3.7-fold and 1.8-fold more cytotoxic than iAs^{III}, respectively.[222] AsHC 332 and AsHC 360 are effective permeability enhancers that would allow other food borne toxicants easy access to the brain.[222] Cytotoxic latency of AsFAs and their water-soluble metabolites were much lower in comparison to iAs^{III} and AsHCs. No substantial cytotoxicities were detected for AsFA 362 [15-(dimethylarsinyl)pentadecanoic acid] or AsFA 388 [17-dimethylarsinyl-9-heptadecenoic acid].[222,251]

Elevated cellular bioavailability in human differentiated neurons, liver, and bladder cells,[61,252] together with the detected increased intestinal bioavailability in the Caco-2 intestinal barrier model,[251] implies that AsHCs appear to effortlessly permeate cell membranes, along with other physiological membranes, which explains how AsHC 332 is able to transport into the brain of *Drosophila melanogaster*;[109] this suggests that these compounds are bioaccessible to the brain.[43,248,253] In the same way, iAs^{III} and DMA^{V} have been demonstrated to traverse the blood-brain barrier in mice and rats.[97–99]

Due to their amphiphilic structure, intact AsLipids are seemingly able to substantially transfer across physiological barriers, such as intestinal barriers[251] and the blood-brain barrier.[253] The blood-brain barrier is a physiological barrier comprising capillary endothelial cells that separates the circulatory system from the brain parenchyma.[222] Interestingly, AsHCs were neither metabolized in the in vitro blood-brain barrier model[222] nor in the in vitro intestinal barrier model.[251] In contrast, arsenolipids present in cod liver oil ingested by humans were biotransformed to small arsenic-containing fatty acids and DMA, which is a similar metabolite for iAs^{III}.[217] AsHCs have been shown to disturb mitochondrial function, leading to decreased cellular ATP levels in fruit flies;[61] while in humans, AsHCs not only reduced the mitochondrial membrane potential but also induced apoptosis, and such effects were not observed with iAs^{III}.[108,254]

A small number of studies have looked into bioaccessibility and metabolism of AsLipids, and the data suggest that AsLipids are swiftly taken in via the gut and, as opposed to AsB, are metabolized before excretion in urine within 6–15 h of consumption.[43] Following ingestion of cod liver oil mainly consisting of AsLipids by two human subjects, more than 85% of the ingested arsenic was eliminated after 2 days. DMA^{V} constituted up to 70% of the arsenic excreted in urine with no intact AsLipids detected.[216,217] Other metabolites included short-chain AsFAs derivatives like dimethylarsenopropanoic acid (DMAPr), dimethylarsenobutanoic acid (DMAB), and their thio-analogues (thio-DMAPr and DMAB).[108,216,217] DMAPr and thio-DMAPr did not trigger any adverse effects in human liver cells (HepG2), human bladder cells (UROtsa), or differentiated neurons.[108,251,252] The fact that AsLipids can occur at high levels in food and have been shown to be bioavailable to humans and extensively degraded to small arsenic species justifies the great interest on the possible toxicities of these compounds.[234]

The latest study performed by Al Amin et al. projected the daily consumption of AsLipids in the Japanese population conducted on 17 food composites, and the results showed that the population is exposed to AsHCs, AsFAs, and AsSugar-PLs.[255] AsLipids were identified mainly in algae, fish, and shellfish of the 17 dietary composites with amounts between 4.4 and 233 ng As/g fresh weight (fw).[255] Of concern was that two AsLipids, AsHC332 and AsHC360, with known cytotoxic effects were identified in algae, fish, and shellfish in amounts in the range of 33–40 ng As/g fw and with an approximated mean daily consumption of about 3000–360 ng As/person/ day or 50–6.0 ng As/kg bw/day. From these findings, it is apparent that diet contributes to the daily intake of toxic AsHC; fortunately, the margin of exposure does not seem to present a health risk with respect to the IC_{50} values of 3.05 and 1.73 μg As/g for human liver and bladder cells exposed to AsHC 332 or AsHC 360, respectively.[61,255]

3. CONSIDERATIONS FOR RISK ASSESSMENT

Seafood is a highly traded and consumed product with implications on commerce and food safety. There is need for regulatory limits based on speciated data, especially for seafood, because data based on total arsenic only as an indicator for risk assessment is inadequate. Detection of arsenic species that exceed regulatory limits can become a technical barrier to trade as was witnessed in 2013 when China imposed a ban on all U.S. imports of geoduck clams (*Panacea generosa*) with an annual value of $80 million.

The European Food Safety Agency (EFSA) provided a risk profile for arsenicals in diet that highlighted the need to legislate in relation to toxic arsenic in food and to generate more speciated arsenic data. Currently, there is no tolerable intake level set for As, since the latest EFSA scientific opinion on As concluded that the previous provisional tolerable weekly intake (PTWI) of 15 μg kg^{-1} bw was no longer appropriate. The EFSA review was an important instrument that stimulated appropriate allocation of resources to more detailed scientific assessments that led to the generation of relevant information. However, this information needs to be systematically collated and evaluated with the objective of establishing regulatory limits, especially for organoarsenicals in seafood, which do not currently have set limits.

The review article by Feldmann et al. highlighted lack of structural and toxicity data on organic arsenic species and suggested the categorization of food samples into three fractions based on the International Agency for Research on Cancer (IARC) classification that classifies all organoarsenicals as potentially toxic. New information has emerged since then with the identification and characterization of some novel organoarsenicals having toxicities like iAs^{III}, a known carcinogen. The molecular structures of more than 50 lipophilic organoarsenicals have been assigned, and new analytical methods have been developed. This information has changed the landscape of risk assessment with respect to organoarsenicals in food, especially seafood.

Risk assessment is a scientifically based process consisting of four main stages, namely, hazard identification, hazard characterization, exposure assessment, and risk characterization. Hazard identification entails the screening process with the purpose of ascertaining the presence of a hazard. For the purpose of this review, a hazard will be defined as a biological or chemical agent capable of causing an adverse health effect and that may be present in a food or group of foods. In the case of arsenic, iAs^{III} is a well-characterized carcinogen. Other toxic arsenicals include arsenic-containing hydrocarbons like AsHC 332, AsHC 360, and AsHC 444, arsenic-containing fatty acids like AsFA 362 and AsFA 388, and methylated trivalent arsenicals like MMA^{III} and DMA^{III}. DMA^{V} is also a known tumor promotor in rat liver.

There is need for more toxicity studies on the new organoarsenicals to identify all the potential sources of hazards. Toxicity studies aim at establishing the severity and frequency of the associated adverse health effect (response). Toxicity studies should not only be limited to the organoarsenicals but also should be extended to their metabolites, because it has been established that most arsenicals are not acutely toxic but that toxicity usually emanates from

metabolic transformations. For example, AsSugars have metabolites similar to iAs^{III}, which is a known carcinogen. There are still many organoarsenicals that have not been tested for toxicity and are assumed to be nontoxic because of the benign nature of some of the known organoarsenicals such as AsB. However, these compounds are not known to be nontoxic. It is therefore imperative that toxicity studies are performed for these recently identified organoarsenicals.

Most arsenic toxicity information was garnered from studies using laboratory animals. This information is important but not necessarily useful in its current form for establishment and/or accurate simulations of regulatory limits. It is therefore imperative that the LD_{50} values obtained from laboratory animals are converted to enforceable limits for human subjects. This call for additional data and information that has been systematically obtained to enable the setting of exposure metrics that can practically be implemented in regulatory practices.

In order to appreciate the exposure level to organoarsenicals, there is need to conduct exposure assessment studies, which entail dietary studies considering the potential sources of exposure with regards to seafood. Exposure assessment requires data from the number of servings of potentially dangerous food ingested (provided from dietary studies) and the level of contamination (provided by information from arsenic speciation analysis), which determines the magnitude of exposure (dose). A few dietary studies have been performed targeting certain foods in different countries. Dose-response assessment links the amount of the hazard ingested (dose) with the chance of developing adverse health effects and the severity of the same. These studies enable the establishment of exposure metrics like PTWI and allowable dietary intake (ADI) which are important in establishing regulatory limits.

The current identification of organoarsenicals have been based on expensive instrumental setups that are beyond the reach of many laboratories. It would be beneficial to have access to an instrument that can concurrently identify and quantify novel organoarsenicals without the need for standards. Even with standards available there is still the challenge of coelutions and isobaric interferences that significantly affect quantification by LC-ICP-MS. There is therefore great need for an element-sensitive detector with a high resolving power and mass accuracy. This will hopefully enable the concurrent identification and detection of organoarsenicals. Such an instrument should be affordable, robust, and with high sensitivity.

The identification of arsenic-containing hydrocarbons (AsHCs), arsenic-containing fatty acids (AsFAs), arsenic-containing fatty alcohols (AsFOHs), and arsenosugar phospholipids (AsPLs) has been aided by high-resolution mass spectrometers with high resolving power and mass accuracy. Mass spectrometers such as the quadrupole ion trap (QITMS), quadrupole time-of-flight (Q-ToFMS), Orbi-trapMS, and Fourier transform ion cyclotron mass spectrometers (FT-ICT-MS) have been used. These instruments are not affordable and require a high level of expertise for operation, which makes them beyond the reach of many laboratories. In addition, the structural information for the identified organoarsenicals need to be confirmed, which requires the use of techniques like nuclear magnetic resonance (NMR) spectroscopy. Additional information can be provided by X-ray crystallography, X-ray absorption near-edge spectroscopy (XANES) or infrared spectroscopy, and mass

spectrometry. Unfortunately, these techniques require analytes at high concentrations, yet the amounts of AsLipids present in the seafood samples are usually very low. Therefore, the arsenicals must be synthesized and characterized in the laboratory for synthetic protocols and characterization of the synthetic products.

It is almost impossible to synthesize standards for all known arsenicals. A pragmatic approach would be to synthesize the standards for arsenicals with known toxicities and to also synthesize their labeled analogues. Due to the monoisotopic nature of arsenic, it is impossible to find labeled As standards. However, for organoarsenicals, the heteroatoms of the synthetic standards can be labeled with ^{13}C or ^{2}H, thus enabling their use as internal standards for identification and quantification of analytes of interest. Concurrent use of these synthetic standards can also be useful in overcoming coelutions and isobaric and polyatomic interferences associated with quantification of organoarsenicals using ICPMS.

There is currently no agreement on a method that is internationally acceptable for arsenic speciation analysis. There is an urgent need for higher-order analytical protocols for the detection and structural assignment, especially for the novel organoarsenicals. There are currently no certified reference materials (CRMs) for the new organoarsenicals. Access to CRMs can be helpful in the validation of analytical methods. Interlaboratory comparisons like proficiency testing (PT) schemes can also provide an additional level of confidence in the measurement results as a tool for assessing the robustness of the validated analytical protocols and for evaluating the equivalence of measurement results.

The concurrent use of the synthetic standards and labeled synthetic standards as internal standard in combination with reliable and robust analytical method for exact quantification of selected arsenicals will play an important role in the establishment of regulatory limits for the toxic organoarsenicals. With reliable analytical methods and availability of standards, development of matrix-matched CRMs will then become a reality.

As an initial step, further effort should be expended in the characterization of lipophilic organoarsenicals in order to obtain a more exhaustive list that can then be tested for toxicity. There is still a lot more to be learnt from the hexane extracts of fatty and oily fish that is mostly discarded because of the high matrix effect. Improvement in the sample cleanup techniques may also allow access to more information from the nonpolar portions of the samples. Another area that might require attention is analysis of samples with high organic content because analysis of intact AsLipids requires them to be dissolved in organic solvents that are not amenable with ICP-MS. The importance of arsenic speciation data cannot be overemphasized. The current approaches for simultaneous identification and quantification will play a critical role in arsenic speciation. Analytical instruments have enabled species identification and structural elucidation; however, there is still need for standards and certified reference materials. These materials will be used for the identification and quantification of arsenolipids in food samples.

Once the hazard identification, hazard characterization, and exposure assessment have been concluded, then the information thereof is used as an input for risk characterization, which is simply the estimation of risk that informs the setting of regulatory limits. Some of the

implementation consid-erations include availability of standards, certified reference materials, validated analytical methods, and established regulatory limits.

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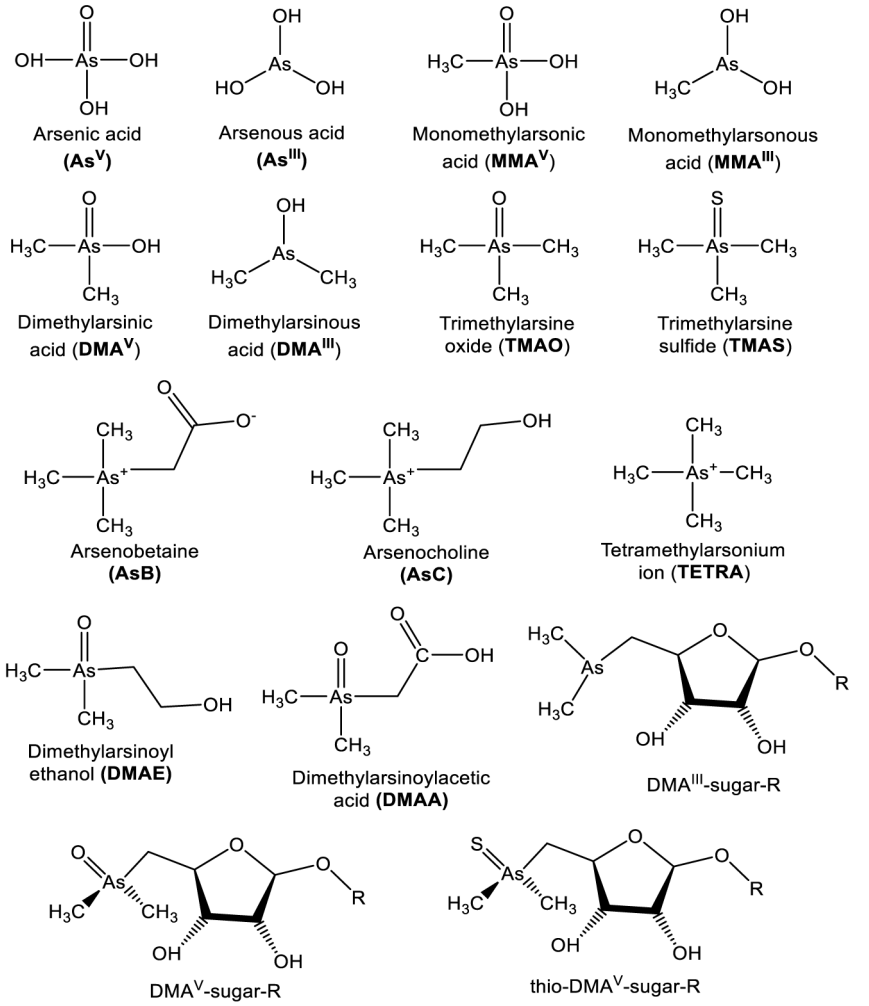

Figure 1.
Structures of common arsenic compounds.

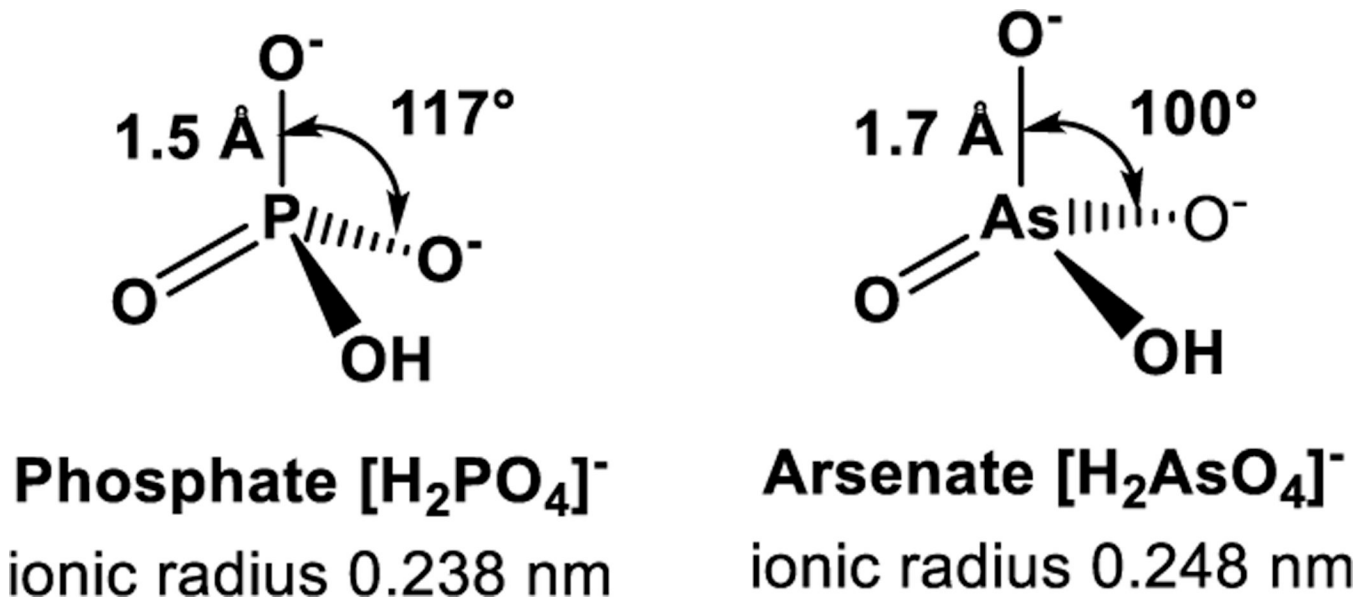

Figure 2.
Structures of deprotonated oxo-anions of arsenate and phosphate.

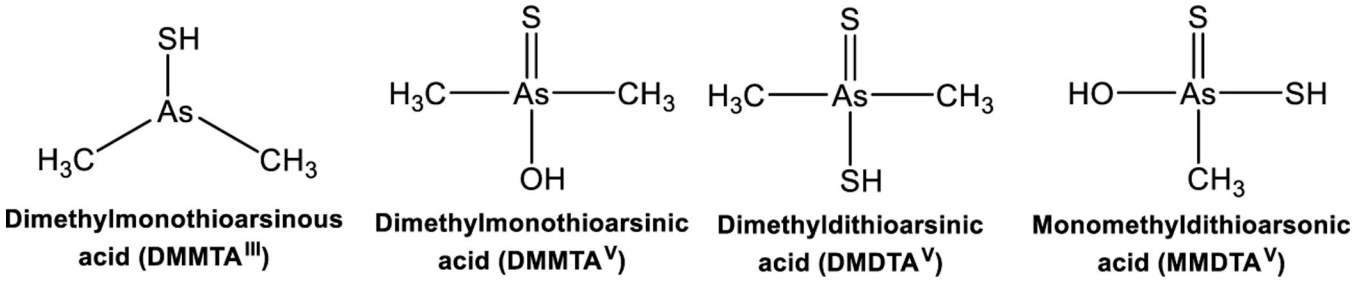

Figure 3.
Structures, names, and abbreviations of methylated thioarsenical compounds.

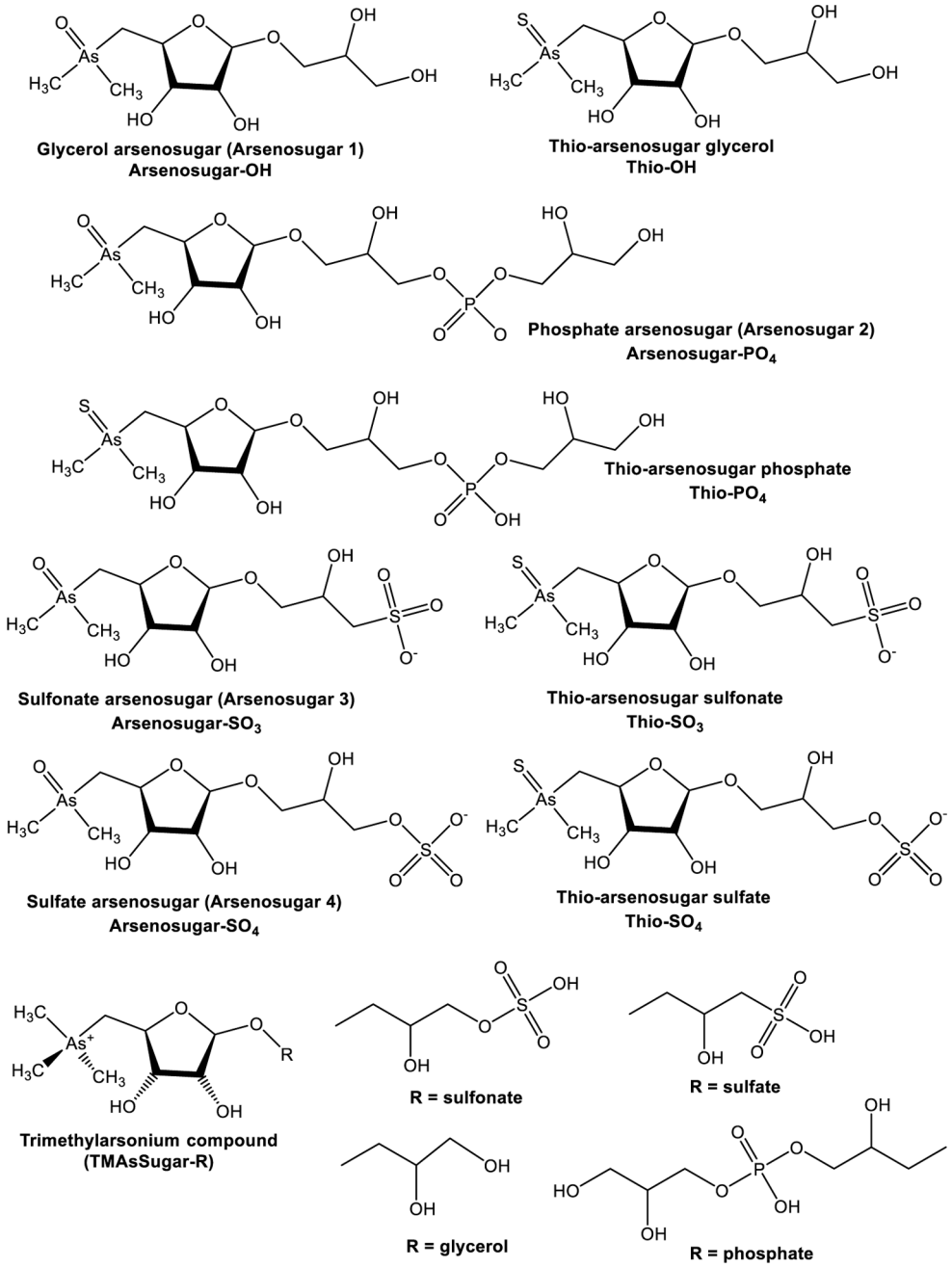

Figure 4.
Structures, names, and abbreviations of arsenosugars.

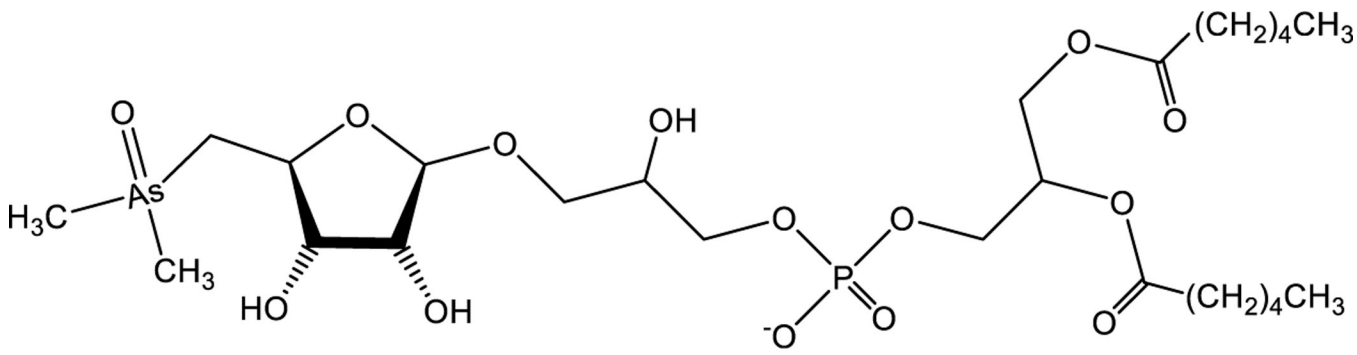

Figure 5.
Chemical structure of lipophilic oxoribofuranoside extracted from the brown algae *U. pinnatifida* (Wakame).

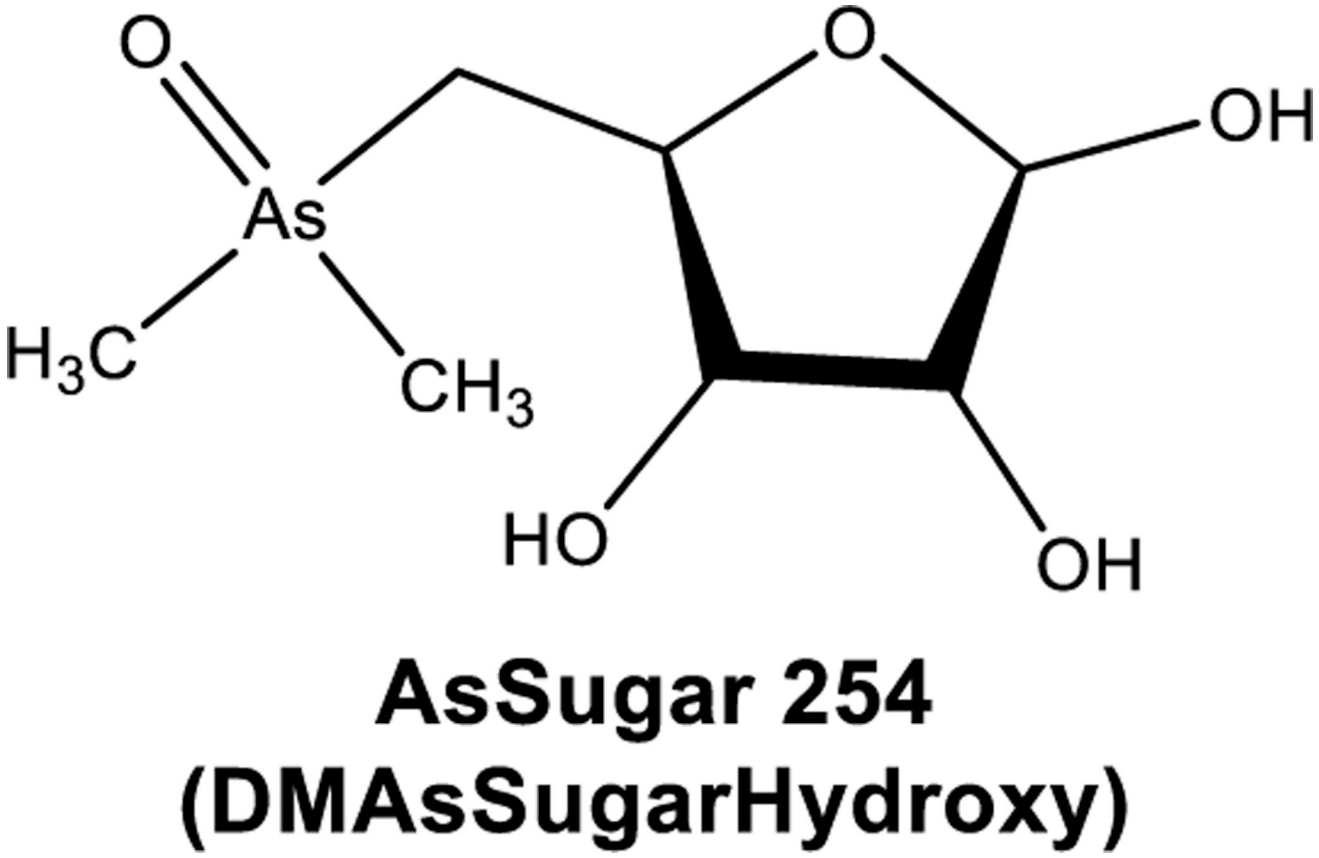

Figure 6.
Structure of AsSugar 254, DMAsSugarHydroxy.

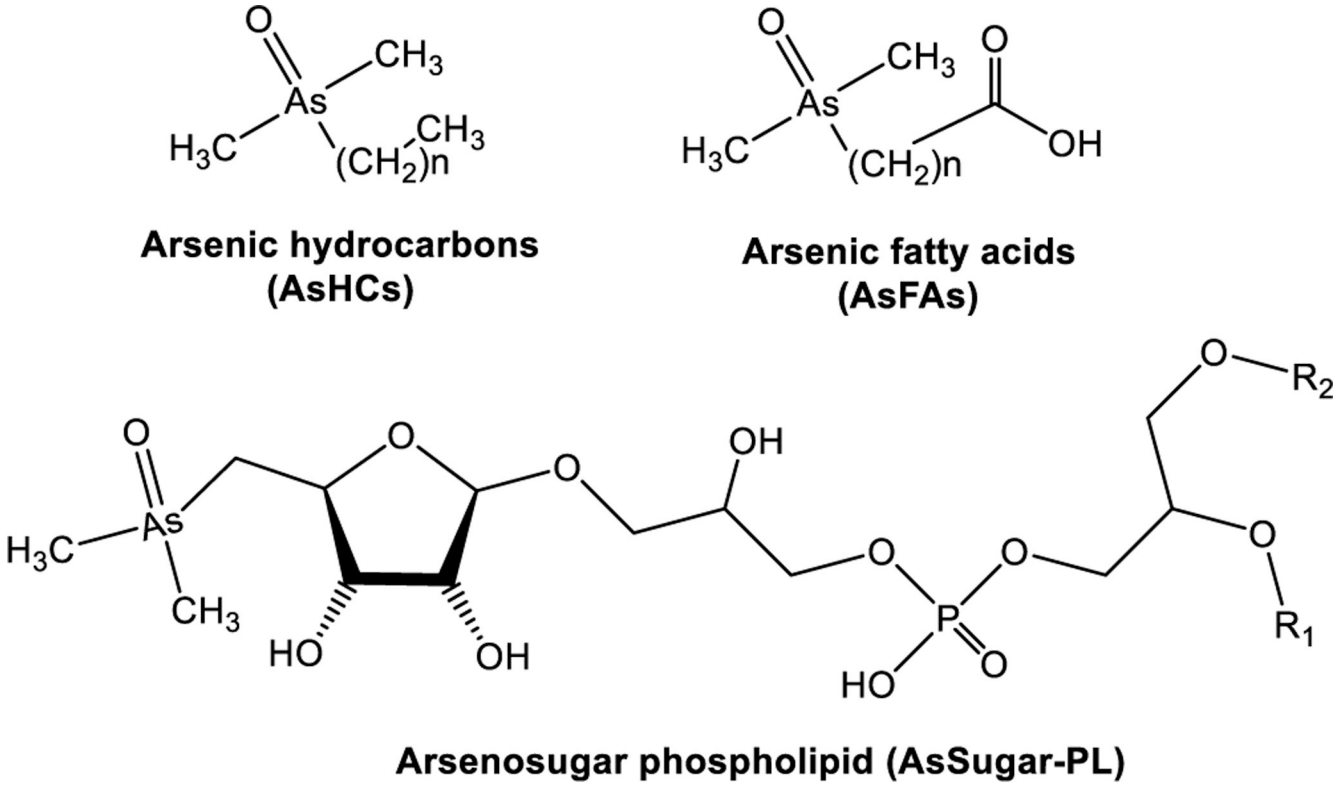

Figure 7.
Structures, names, and abbreviations of arsenolipids.

Table 1.

Experimental Biological Activities of Different Arsenicals

no.	arsenic species	LD_{50} (mg kg^{-1})[a]	animal	ref
1	MMA^{III}	2	mice	Petrick et al.[158]
2	MMA^{V}	916	mice	Kaise et al.[150]
3	DMA^{V}	648	mice	Kaise et al.[150]
4	AsC	6500	mice	Kaise et al.[152]
5	AsB	> 10000	mice	Kaise et al.[64]
6	TMAO	5500	mice	Kaise et al.[150]
7	TETRA as TMA-chloride	890	mice	Shiomi et al.[159]
8	TETRA as TMA-hydroxide	no toxicity	mice	Sakurai et al.[160]
9	$DMAs^{III}$-sugar-glycerol	6.56×10^{-2}[b]	human UROtsa	Andrewes et al.[21]
10	$DMAs^{V}$-sugar-glycerol	1.968[b]	human UROtsa	Andrewes et al.[21]
11	AsHC 332	3.25×10^{-3}[b]	human UROtsa	Meyer et al.[61]
12	AsHC 360	1.73×10^{-3}[b]	human UROtsa	Meyer et al.[61]
13	AsHC 444	2.31×10^{-3}[b]	human UROtsa	Meyer et al.[61]

[a] LD_{50}: Concentration at which 50% of a population dies.

[b] IC_{50}: Concentration at which the cell viability is reduced by 50%.