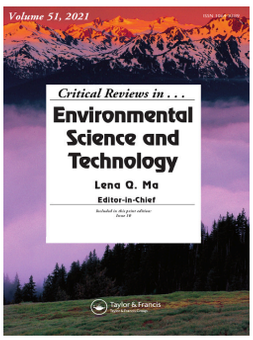

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The enigma of environmental organoarsenicals

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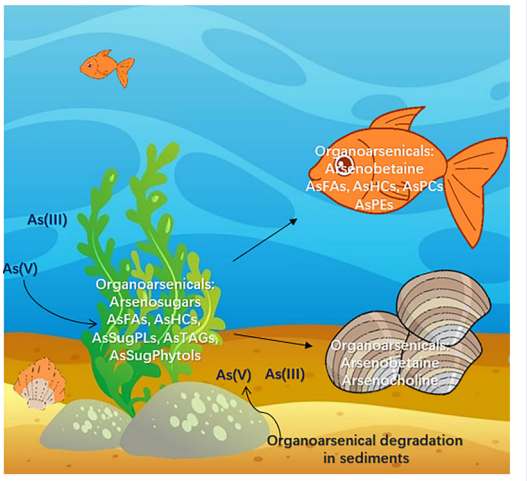
ABSTRACT

Over 300 species of naturally occurring-organoarsenicals have been identified with the development of modern analytical techniques. Why there so many environmental organoarsenicals exist is a real enigma. Are they protective or harmful? Or are they simply by-products of existing pathways for non-arsenical compounds? Fundamental unanswered questions exist about their occurrence, prevalence and fate in the environment, metabolisms, toxicology and biological functions. This review focuses on possible answers. As a beginning, we classified them into two categories: water-soluble and lipid-soluble organoarsenicals (arsenolipids). Continual improvements in analytical techniques will lead to identification of additional organoarsenicals. In this review, we enumerate identified environmental organoarsenicals and speculate about their pathways of synthesis and degradation based on structural data and previous studies. Organoarsenicals are frequently considered to be nontoxic, yet trivalent methylarsenicals, synthetic aromatic arsenicals and some pentavalent arsenic-containing compounds have been shown to be highly toxic. The biological functions of some organoarsenicals have been defined. For example, arsenobetaine acts as an osmolyte, and membrane arsenolipids have a phosphate-sparing role under phosphate-limited conditions. However, the toxicological properties and biological functions of most organoarsenicals are largely unknown. The objective of this review is to summarize the toxicological and physiological properties and to provide novel insights into future studies.



KEYWORDS Arsenic; arsenolipids; arsenic toxicity; physiological functions of organoarsenicals; water-soluble organoarsenicals

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Supplemental data for this article can be accessed at publisher's website.

Introduction

The majority of arsenic exists as arsenic-containing minerals such as sulfide or iron minerals in Earth's crust (Zhu et al., 2014). Inorganic arsenic is readily taken up adventitiously via transport systems for essential nutrients. Trivalent arsenite As(III) is taken into cells by a variety of membrane transporters including aquaglyceroporin channels (Liu et al., 2002), glucose permeases (Jiang et al., 2010), hexose transporters (Liu et al., 2004) and inositol permeases (Duan et al., 2016). Pentavalent arsenate As(V) is accumulated via several different phosphate transporters (Yan et al., 2017). Arsenic is often bio-transformed into organoarsenicals by microbes, presumably for detoxification or utilization. Arsenic methylation can serve as a detoxification process, especially in an oxic environment, because the trivalent methylated arsenicals that are produced are rapidly oxidized to the nontoxic pentavalent species in air (Ye et al., 2012). Arsenobetaine is nontoxic and confers resistance against osmotic stress and temperature extremes to bacteria (Hoffmann et al., 2018). However, the idea that organoarsenicals are less toxic than inorganic arsenic has been gradually reevaluated since trivalent methylarsenicals were demonstrated to be extremely toxic (Aposhian et al., 2001). Furthermore, some arsenic-containing hydrocarbons (AsHCs) have been shown to be more cytotoxic on human liver and bladder cells than As(III) (Meyer et al., 2014b) and can cross the blood-brain barrier of *Drosophila melanogaster* and *in vitro* intestinal barrier models (human intestinal Caco-2 cells) (Meyer et al., 2015; Niehoff et al., 2016). Additional novel arsenolipid species have been identified (Freitas et al., 2020; Glabonjat et al., 2019b; Řezanka et al., 2019), and more arsenolipid species undoubtedly remain to be identified. However, little is known about arsenolipids besides their structures, in part because they are found mainly in marine organisms that host various symbionts and parasites. The discussion about the biosynthetic pathway and possible biological functions of organoarsenicals, and the complete summary of detected arsenolipids distinguishes our review paper from others. In the previous reviews, Luvonga et al. focused on the assessment of human exposure to arsenic from seafood (Luvonga et al., 2020). Chen et al. focused on the toxicology and biotransformation of organoarsenicals, emphasizing water-soluble arsenicals, aromatic organoarsenicals, and described about 50 natural arsenolipids (Chen et al., 2020a) compared with 260 natural arsenolipids described here. In this review, we summarize the properties of most naturally occurring-organoarsenicals identified to date, the organisms in which they are found, their biosynthetic and degradation pathways and toxicity, as well as potential functions. Finally, we present a series of questions that remain unanswered and will provide direction for future research in this field.

The species of natural occurring organoarsenicals in the environment

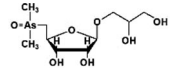
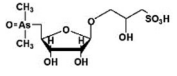
More than 300 species of naturally occurring-organoarsenicals have been identified to date. They are divided operationally into two broad categories, water-soluble and lipid-soluble organoarsenicals (arsenolipids). The former is soluble in aqueous solutions, while the latter is insoluble in water but soluble in less-polar organic solvents.

Water-soluble organoarsenicals

Simple methylated arsenicals

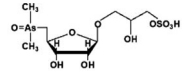
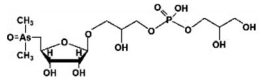
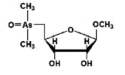
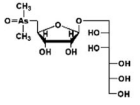
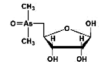
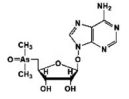
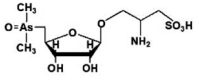
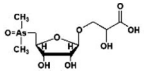
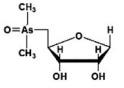
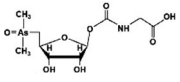
Gosio gas liberated from moldy wallpaper colored with arsenic-containing pigments was identified as tri-methylarsine (Table 1.1) in 1933 (Challenger et al., 1933), marking the beginning of the study of biological methylation of arsenic. Mono- (Table 1.2 and 1.3), di- (Table 1.4 and 1.5), or tri-methylated arsenicals (Table 1.1 and 1.6) are generated by fungi (Challenger et al., 1933), bacteria (Qin et al., 2006), archaea (Wang et al., 2014), algae (Qin et al., 2009), cyanobacteria (Yin et al., 2011a), protozoan (Yin et al., 2011b), marine organisms (Foster, 2007), mouse and

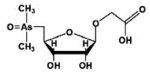
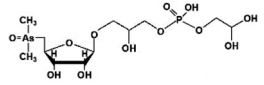
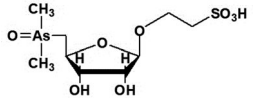
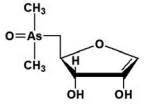
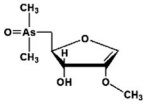
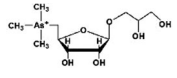
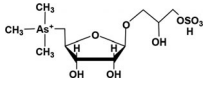
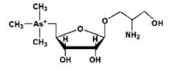
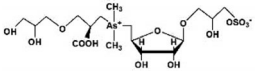
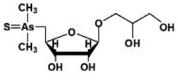
Table 1. Full names, abbreviation and chemical structures of organoarsenicals described in this review.

			full names of arsenic compounds	abbreviation	Chemical structure
Water-soluble arsenicals	Simple methylated arsenicals	1	trimethylarsine	TMAs	
		2	monomethylarsonous acid	MAs(III)	
		3	monomethylarsonic acid	MAs(V)	
		4	dimethylarsonous acid	DMAs(III)	
		5	dimethylarsonic acid	DMAs(V)	
		6	trimethylarsine oxide	TMAO	
		7	monomethylarsine	MAs	
		8	dimethylarsine	DMAs	
		9	monomethylmonothioarsonic acid	MMMTAs(V)	
		10	monomethyldithioarsonic acid	MMDTAs(V)	
		11	monomethyltrithioarsonic acid	MMTTAs(V)	
		12	dimethylmonothioarsinic acid	DMMTAs(V)	
		13	dimethyldithioarsinic acid	DMDTAs(V)	
		14	trimethylarsine sulfide	TMAS	
		15	tetramethylarsonium ion	TETRA	
	arsenosugars	16	2′, 3′-dihydroxypropyl 5-deoxy-5-dimethylarsinoyl-β-D-riboside	Oxo-Gly	
		17	2′-hydroxy-3′-sulfonylpropyl 5-deoxy-5-dimethylarsinoyl-β-D-riboside	Oxo-SO_3	

(*continued*)

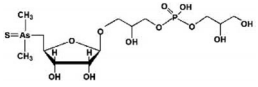
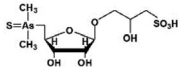
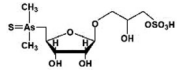
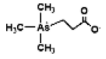
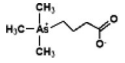
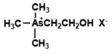
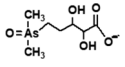
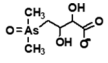
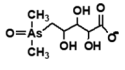
Table 1. Continued.

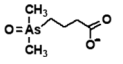
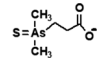
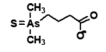
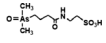
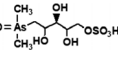
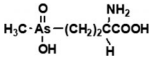
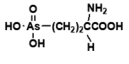
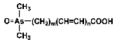
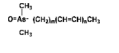
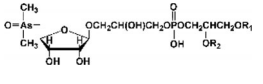
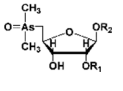
		full names of arsenic compounds	abbreviation	Chemical structure
	18	2′-hydroxy-3′-sulfooxypropyl 5-deoxy-5-dimethylarsinoyl-β-D-riboside	Oxo-SO_4	
	19	3′-[(2′′,3′′-dihydroxypropyl) hydroxyphosphinyloxy]-2′-hydroxypropyl 5-deoxy-5-dimethylarsinoyl-β-D-riboside	Oxo-PO_4	
	20	methyl 5-deoxy-5-(dimethylarsinoyl)-β-D-riboside		
	21	1-O-[5′-deoxy-5′-(dimethylarsinoyl)-β-D-ribosyl] mannitol		
	22	5-deoxy-5-(dimethylarsinoyl)-β-D-riboside		
	23	5′-deoxy-5′-dimethylarsinoyladenosine	DDMAA	
	24	2-amino-3-[5-deoxy-5-dimethylarsinoyl-β-D-ribofuranosyloxy]propane-1-sulfonic acid		
	25	3-(5′-deoxy-5′-dimethylarsinoyl-β-D-ribosyloxy)-2-hydroxypropanoic acid		
	26	5-dimethylarsinoyl-β-ribofuranose		
	27	N-(5′-deoxy-5′-dimethylarsinoyl-β-Dribosyloxycarbonyl)glycine		

28	2-(5′-deoxy-5′-dimethylarsinoyl-β-D-ribosyloxy)-ethanoic acid		
29	3-[5′-deoxy-5′-(dimethylarsinoyl)-β-ribofuranosyloxy]-2-hydroxypropyl 2, dihydroxyethyl phosphate		
30	2-[5-deoxy-5-dimethylarsinoyl-β-D-ribofuranosyloxy]ethane-1-sulfonic acid		
31	dehydroxy-5-deoxy-5-(dimethylarsinoyl)-β-D-riboside		
32	2-*O*-methyl dehydroxy-5-deoxy-5-(dimethylarsinoyl)-β-D-riboside		
33	2-*O*-methyl-5-deoxy-5-(dimethylarsinoyl)-β-D-riboside		
34	2′, 3′-dihydroxypropyl 5-deoxy-5-trimethylarsinoyl-β-D-riboside	TriMe-Gly	
35	2′-hydroxy-3′-sulfooxypropyl 5-deoxy-5-trimethylarsinoyl-β-D-riboside	TriMe-SO_4	
36	2′-amino- 3′-hydroxypropyl 5-deoxy-5-trimethylarsinoyl-β-D-riboside		
37	2′-hydroxy-3′-sulfonylpropyl 5-deoxy-5-[3′-(2′,3′-dihydroxypropoxy)-2′-methylpropanoic acid]-dimethylarsinoyl-β-D-riboside		
38	2′, 3′-dihydroxypropyl 5-deoxy-5-dimethylarsinothioyl-β-D-riboside	Thio-Gly	

(*continued*)

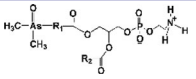
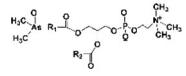
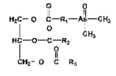
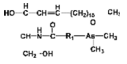
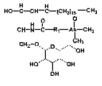
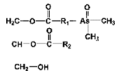
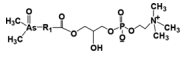
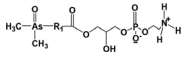
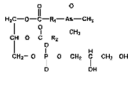
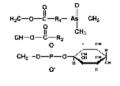
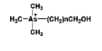
Table 1. Continued.

		full names of arsenic compounds	abbreviation	Chemical structure
	39	3′-[(2′′,3′′-dihydroxypropyl) hydroxyphosphinyloxy]-2′-hydroxypropyl 5-deoxy-5-dimethylarsinothioyl-β-D-riboside	Thio-PO_4	
	40	2′-hydroxy-3′-sulfonylpropyl 5-deoxy-5-dimethylarsinothioyl-β-D-riboside	Thio-SO_3	
	41	2′-hydroxy-3′-sulfooxypropyl 5-deoxy-5-dimethylarsinothioyl-β-D-riboside	Thio-SO_4	
Arsenobetaine, and arsenocholine and their homologs	42	arsenobetaine		
	43	trimethylarsoniopropionate	TMAP	
	44	trimethylarsoniobutyrate	TMAB	
	45	arsenocholine		
	46	homoarsenocholine		
	47	arsenocholine-*O*-sulfate		
Other water-soluble organoarsenicals	48	5-dimethylarsinoyl-2,3-dihydroxypentanate		
	49	4-dimethylarsinoyl-2,3-dihydroxybutanate		
	50	5-dimethylarsinoyl-2,3,4-trihydroxypentanate		

	51	dimethylarsinoylacetic acid	DMAA	
	52	dimethylarsinoylethanol	DMAE	
	53	dimethylarsenopropanoic acid	DMAP	
	54	4-dimethylarsinoyl butanoic acid	DMAB	
	55	dimethylarsinothioylacetic acid	Thio-DMAA	
	56	dimethylarsinothioylethanol	Thio-DMAE	
	57	dimethylarsoniothioylpropanoic acid	Thio-DMAP	
	58	4-dimethylarsinothioyl butanoic acid	Thio-DMAB	
	59	N-[4-(dimethylarsinoyl) butanoyl]taurine		
	60	1-deoxy-1-dimethyl-arsinoylribitol-5-sulfate		
	61	2-amino-4-(hydro- xymethylarsinoyl)butanoic	AST	
	62	2-amino-4-(dihydroxyarsonoyl) butanoic acid	AST-OH	
Lipid-soluble arsenicals	63	arsenic-containing fatty acids	AsFAs	
	64	arsenic-containing hydrocarbons	AsHCs	
	65	arsenosugar phospholipids	AsSugPLs	
	66	phytyl 2-*O*-methyl dimethylarsinoyl riboside	AsSugPhytols	

(*continued*)

Table 1. Continued.

		full names of arsenic compounds	abbreviation	Chemical structure
AsFA-containing lipids	67	arsenic-containing phosphatidyethanolamines	AsPEs	
	68	arsenic-containing phosphatidylcholines	AsPCs	
	69	arsenic-containing triacylglycerols	AsTAGs	
	70	arsenic-containing ceramides	AsCers	
	71	arsenic-containing hexosylceramide	AsHexCers	
	72	arsenic-containing diacylglycerols	AsDAGs	
	73	arsenic-containing Lyso-phosphatidylcholines	AsLPCs	
	74	arsenic-containing Lyso-phosphatidylethanolamines	AsLPEs	
	75	arsenic-containing phosphatidylglycerols	AsPGs	
	76	arsenic-containing phosphatidylinositols	AsPIs	
Other minor arsenolipids	77	trimethylarsenio fatty alcohols	TMAsFOH	

humans (Vahter, 1999). Arsenic was volatilized as mono- (Table 1.7), di- (Table 1.8), or tri-methylarsine under anaerobic conditions (Mestrot et al., 2013). In contrast, flowering plants other than algae are unable to methylate arsenic (Lomax et al., 2012), and methylarsenicals in flowering plants are likely produced by rhizosphere or endophytic microbes (Zhang et al., 2017). Recently, thiolated methylarsenicals (Table 1.9-1.14) have attracted attention because of their wide occurrence in paddy soils (Kerl et al., 2019), animal urine and tissues (Sun et al., 2016). Tetramethylarsonium ion (Table 1.15) is commonly found in marine invertebrates, particularly in clams where it is the major form (Cullen & Dodd, 1989). It is not clear whether thiolation is abiotic or enzyme catalyzed.

Arsenosugars

Arsenosugars have a di- or tri-methylarsinoyl moiety, in which pentavalent arsenic binds to two or three methyl group substituents, to oxygen or sulfur and to a deoxyribose sugar with different side chains on its C1 position. Although arsenicals found in marine algae were termed as organoarsenicals (Jones, 1922), no organoarsenicals, other than mono- or di-methylarsine and arsenobetaine (Table 1.42), were identified until 1981, when two arsenosugars, 2′, 3′-dihydroxypropyl 5-deoxy-5-dimethylarsinoyl-β-D-riboside (Oxo-Gly, Table 1.16) and 2′-hydroxy-3′-sulfonylpropyl 5-deoxy-5-dimethylarsinoyl-β-D-riboside (Oxo-SO_3, Table 1.17), were identified in the eukaryotic brown macroalga *Ecklonia radiate* (Edmonds & Francesconi, 1981). Since then, nearly 30 naturally occurring arsenosugars and structural isomers have been identified from organisms (Table 1.16-1.41), including prokaryotic cyanobacteria and eukaryotic algae. The distribution of arsenosugars varies depending on algal types. The major arsenosugars in brown algae are dimethylarsenoribosides such as Oxo-SO_3 and 2′-hydroxy-3′-sulfooxypropyl 5-deoxy-5-dimethylarsinoyl-β-D-riboside (Oxo-SO_4, Table 1.18), whereas Oxo-Gly and 3′-[(2″,3″-dihydroxypropyl)-hydroxyphosphinyloxy]-2′-hydroxypropyl 5-deoxy-5-dimethylarsinoyl-β-D-riboside (Oxo-PO_4, Table 1.19) predominate in eukaryotic red and green algae (Francesconi & Edmonds, 1998). Oxo-Gly and Oxo-PO_4 were also found in prokaryotic freshwater cyanobacteria (Xue et al., 2014, Xue et al., 2017a). Rare dimethylarsenoribosides species were identified in the brown alga *Sargassum lacerifolium* (Table 1.20-1.22) (Francesconi et al., 1991), the kidneys of *Tridacna* genus (Table 1.22-1.30) (Francesconi et al., 1992; McSheehy et al., 2002b; Nischwitz & Pergantis, 2007), the planktons from Mono Lake (Table 1.31) (Glabonjat et al., 2020), and the eukaryotic unicellular alga *Dunaliella teriolecta* (Table 1.32 and 1.33) (Glabonjat et al., 2018).

In addition to dimethylarsenoribosides, four trimethylarsonioribosides have been found in the clam *Tridacna maxima* (Table 1.34 and 1.35) (Nischwitz & Pergantis, 2007), a *Laminaria* brown macroalga (Table 1.36) (McSheehy et al., 2002a), *Sargassum thunbergii* (Table 1.37) (Francesconi et al., 1991). In addition, identification of sulfur-containing dimethylarsenoribosides was another remarkable discovery. Thiol analogs of the four common arsenosugars (Table 1.38-1.41) have been found in *T. maxima* (Nischwitz & Pergantis, 2007) and the marine alga *Fucus vesiculosus* (Meier et al., 2005).

Arsenobetaine, arsenocholine and their homologs

Arsenobetaine (Table 1.42) was identified from the tail muscle of the western rock lobster *Panulirus longipes cygnus* (Edmonds et al., 1977). Arsenobetaine is the major arsenic species in many herbivorous animals, accounting for $70-100\%$ of total arsenic in lean fish (Súñer et al., 2002) and lobster (Grinham et al., 2014). Arsenobetaine has also been detected in marine macroalgae (Zhao et al., 2020) and mushrooms (Li et al., 2019). Two forms of arsenobetaine were also identified in the marine fish *Abudefduf vaigiensis* (Table 1.43) (Francesconi et al., 2000) and the blue mussel *Mytilus edulis* (Table 1.44) (Francesconi et al., 1999). Arsenocholine (Table 1.45) can be transformed into arsenobetaine (Hoffmann et al., 2018), and is often detected in organisms

that generate arsenobetaine. The arsenic-containing compound, homoarsenocholine (Table 1.46), was detected in a macrofungi *Ramaria* genus, where arsenobetaine accounted for 84% of the total extracted arsenic with small amounts of methylarsonic acid (MAs(V), Table 1.3), dimethylarsonic acid (DMAs(V), Table 1.5), trimethylarsine oxide (Table 1.14), tetramethylarsonium ion, trimethylarsoniopropinate (Table 1.43) and arsenocholine (Braeuer et al., 2018). More recently, arsenocholine-*O*-sulfate (Table 1.47) was identified as a major arsenic species in the mushroom *Tolypocladium ophioglossoides* (Braeuer et al., 2021).

Other water-soluble organoarsenicals

Complex organoarsenicals are not accumulated along the food chains, suggesting that a portion is degraded in higher trophic animals. Compounds containing a dimethylarsinoyl moiety and a carboxy group (Table 1.48-1.51) have been identified in the kidney of *Tridacna derasa* that hosts symbiotic algae in its tissues (McSheehy et al., 2002b). Presumably these compounds are degradation products of arsenosugars or other organoarsenicals. Dimethylarsinoylacetic acid (DMAA, Table 1.51), dimethylarsinoylethanol (DMAE, Table 1.52), dimethylarsenopropanoic acid (Table 1.53), 4-dimetylarsinoyl butanoic acid (Table 1.54), and the corresponding thio-arsenic compounds (Table 1.55-1.58) have all been identified as minor arsenicals in human urine after ingestion of blue mussels (Molin et al., 2012). N-[4-(Dimethylarsinoyl)butanoyl]taurine (Table 1.59) has been found in the kidney of *T. maxima* (Francesconi et al., 1992). 1-Deoxy-1-dimethylarsinoylribitol-5-sulfate (Table 1.60), the major arsenic compound identified in the red alga *Chondria crassicaulis*, is widely distributed in red algae (Edmonds et al., 1997).

Burkholderia gladioli strain GSRB05 converts As(III) into two novel organoarsenicals, 2-amino-4-(hydroxymethylarsinoyl)butanoate, or arsinothricin (Table 1.61) and its likely precursor, 2-amino-4-(dihydroxyarsonoyl)butanoic acid, or hydroxyarsinothricin (Table 1.62) (Kuramata et al., 2015). Arsinothricin is an arsenic mimetic of the phosphonate antibiotic 2-amino-4-(hydroxymethylphosphinyl) butanoate, or phosphinothricin produced by *Streptomyces* species and widely used commercially as an herbicide. In arsinothricin the phosphorus atom is replaced by an arsenic atom, the arsenate equivalent of a phosphonate. Arsinothricin is an effective broad-spectrum antibiotic against both Gram-negative and Gram-positive bacteria, including some of the most life-threatening pathogens. It is an analog of the γ-phosphoglutamate intermediate in the glutamine synthetase reaction. Its mechanism of action is via inhibiting glutamine synthetase, presumably by specific binding to the active site during the catalytic cycle and preventing formation of the γ-phosphoenzyme intermediate (Nadar et al., 2019). In addition to the natural product arsinothricin, arsenicals have been used as medicines since the eras of ancient Greece and China. Synthetic aromatic arsenicals are still in use today as effective therapeutics for humans and livestock animals (Zhu et al., 2002). In the future, we can anticipate that additional organoarsenicals with antibiotic or therapeutic activity will be discovered and utilized to design and develop novel drugs.

Lipid-soluble organoarsenicals

Marine algae and animals accumulate and transform arsenic directly from ambient water or from food chain, containing water-soluble organoarsenicals and arsenolipids, with total concentrations ranging from 1 to more than 100 mg As kg^{-1} (dry mass) (Edmonds & Francesconi, 2003). Although as early as the 1920s arsenolipids were reported in cod-liver (Sadolin, 1928), the first structures of arsenosugar phospholipids (AsSugPLs) were not determined until 1988 (Morita & Shibata, 1988). So far more than 260 arsenolipids have been identified, falling into six distinct groups.

Arsenic-containing fatty acids (AsFAs)

AsFAs are the derivatives of saturated or unsaturated fatty acids where the end methyl group is replaced with a dimethylarsinoyl group (Table 1.63). Since the first identification of AsFAs species from cod-liver oil (Rumpler et al., 2008), over 50 species with a carbon chain ranging from C5 to C30 have been identified from marine fish or algae (Table S1). Whether AsFAs are synthesized by bacteria, algae, animals, or a combination of those has not been determined. The Mediterranean mussel *Mytilus galloprovincialis* does not catalyze elongation of non-arsenic fatty acids but contain AsFAs with very long-chain fatty acids (>C22). This observation suggests that the arsenic-containing compounds were derived from ingested bacteria (Freitas et al., 2020).

Arsenic-containing hydrocarbons (AsHCs)

AsHCs (Table 1.64), naturally occurring compounds with an arsenic-containing polar head and a hydrophobic tail, was first discovered in the oil from plankton-feeding marine fish capelin (*Mallotus villosus*) (Taleshi et al., 2008). Nearly 20 species of AsHCs have been identified in marine algae, fish oil, herring caviar, and even fish brain (Table S2). The carbon chain length in AsHCs ranges between 15 and 31, with AsHC 332 (C15:0) and AsHC 360 (C17:0) being the most common forms. Based on the observations that AsHCs can pass through the intestinal barrier *in vitro* models (human intestinal Caco-2 cells) and the blood brain-barrier (porcine brain capillary endothelial cells) essentially unchanged, uptake by passive diffusion has been proposed (Meyer et al., 2015; Müller et al., 2018), although the existence of a transport protein cannot be ruled out.

Mono/di-acyl arsenosugar phospholipids (AsSugPLs)

AsSugPL 958 is the first arsenolipid with its structure determined (Morita & Shibata, 1988). Since its report in 1988, more than 40 species of AsSugPLs have been identified from brown algae, cyanobacteria, and fish caviars (Table S3). Mono- and di-acyl AsSugPLs both comprise three main building blocks: the Oxo-Gly head-group, the esterified phosphoryl glycerol, and one or two fatty acids (Table 1.65). Five major AsSugPLs (958, 986, 1014, 1042, and 1070) in the brown macroalga *Sargassum fusiforme*, also known as *Hijiki*, were quantified using the certified reference material CRM 7405-a, indicating that the brown alga contained much higher concentrations of AsSugPL 958 compared with the other four AsSugPLs (Glabonjat et al., 2014). The brown macroalgae *Saccharina latissima* and *Alaria esculenta* also contain more AsSugPLs in younger metabolically active thallus tissues than in older tissues (Pétursdóttir et al., 2019).

Phytyl 2-O-methyl/2-hydroxy dimethylarsinoyl ribosides (AsSugPhytols)

AsSugPhytols are ether-bound phytyl 2-*O*-methyl/2-hydroxy arsenosugars (Table 1.66 and S4) that have been detected in pure cultures of the unicellular alga *Dunaliella tertiolecta* (Glabonjat et al., 2017), the photoautotrophic picoplankter *Picocystis* strain ML (Glabonjat et al., 2020), and algal detritus-rich sediments from the Great Salt Lake (Glabonjat et al., 2019b). AsSugPhytols are the only naturally occurring compounds containing 2-*O*-methylribosides outside the RNA world, where incorporation of 2-*O*-methyl RNA bases in tRNA or miRNA increases their stability and improves their affinity to target mRNA (Majlessi et al., 1998; Pasternak et al., 2007). Moreover, the phytol constituent of AsSugPhytols is proposed to perform a similar function as phytol in chlorophyll-a, anchoring the molecule in the membrane of the chloroplast to improve the membrane stability (Glabonjat et al., 2017).

ASFA-containing lipids

The arsenic-containing phosphatidylethanolamine (AsPE, Table 1.67 and S5) was identified in salmon caviar, and another group of arsenic-containing phosphatidylcholines (AsPCs, Table 1.68

and S6) was found in herring caviar (Viczek et al., 2016). A total of 98 types of arsenolipids were identified in the green alga *Coccomyxa*, consisting of 7 AsFAs, 8 AsPEs, 15 AsPCs, 39 arsenic-containing triacylglycerols (AsTAGs, Table 1.69 and S7), 3 arsenic-containing ceramides (AsCers, Table 1.70 and S8B), 2 arsenic-containing hexosylceramides (AsHexCers, Table 1.71 and S8C), 7 arsenic-containing diacylglycerols (AsDAGs, Table 1.72 and S8D), 5 arsenic-containing lyso-phosphatidylcholines (AsLPCs, Table 1.73 and S8E), 4 arsenic-containing lyso-phosphatidylethanolamines (AsLPEs, Table 1.74 and S8F), 2 arsenic-containing phosphatidylglycerols (AsPGs, Table 1.75 and S8G), and 6 arsenic-containing phosphatidylinositols (AsPIs, Table 1.76 and S8H) (Řezanka et al., 2019). These arsenolipids consist of common classes of lipids such as phosphatidylethanolamine, phosphatidylcholine, triacylglycerol, ceramide, hexosylceramide, diacylglycerol, lyso-phosphatidylcholine, lyso-phosphatidylethanolamine, phosphatidylglycerol and phosphatidylinositol, where one of the fatty acids is replaced with an AsFA. It is likely that additional AsFAs-containing lipids remain to be identified.

Other minor arsenolipids

In addition to the major arsenolipid groups we discussed above, there were several minor arsenolipid groups present in various marine sources, such as trimethylarsenio fatty alcohols (Table 1.77 and S8A) identified in the brown microalga *S. latissima* (Pétursdóttir et al., 2019). One new arsenolipid, arseno-ether-phospholipid (AsEP 734, Table S8I), was identified in the digestive gland and mantle of *M. galloprovincialis* (Freitas et al., 2020). Glycerylphosphorylarsenocholine and phosphatidylarsenocholine (Table S8J) were found in the yelloweye mullet *Aldrichetta forstert* fed arsenocholine (Francesconi et al., 1990). The development of modern analytical technology will extend our knowledge of complex organoarsenicals.

Biosynthesis and degradation of organoarsenicals

Recently, thirteen gene families involved in bacterial arsenic resistance were examined by molecular clock analysis (Chen et al., 2020b). The results suggest that the *arsM* gene encoding the enzyme As(III) *S*-adenosylmethionine methyltransferase (ArsM) evolved in an anoxic world earlier than the other genes, including those for regulatory proteins and transporters. Given that MAs(III) and DMAs(III), the predicted major products of ArsM under the anoxic condition on the primitive Earth, are much more toxic than As(III), those compounds may have been produced to serve as primordial antibiotics. Only after the Great Oxidation Event, were they oxidized into the relatively benign complex pentavalent species, changing ArsM from an enzyme of antibiotic synthesis to one of detoxification.

Synthesis and degradation of methylated arsenicals

The most thoroughly characterized mechanisms for arsenical biotransformation are arsenic methylation and demethylation. In 2006, ArsM from the soil bacterium *Rhodopseudomonas palustris* was characterized both *in vivo* and *in vitro* using heterologous expression in *Escherichia coli* and purified protein to catalyze sequential methylation of As(III), producing mono-, di- and trimethylated species with tri-methylarsine gas as the end product (Fig. 1A) (Qin et al., 2006). ArsM orthologs have been identified in eukaryotes, including metazoan, fungi, and algae, where *arsM* genes were acquired horizontal gene transfer between different kingdoms of life (Chen et al., 2017). AS3MT from humans and mice are ArsM orthologs involved in arsenic methylation. Crystal structures of CmArsM, the ArsM ortholog from the thermophilic eukaryotic red alga *Cyanidioschyzon merolae*, were solved with no ligands (Ajees et al., 2012), with bound *S*-adenosylmethionine (SAM) (Ajees et al., 2012), As(III) (Ajees et al., 2012), MAs(III) (Packianathan et al.,

2018a), phenylarsenite (Packianathan et al., 2018a), trivalent roxarsone (Packianathan et al., 2018a), or with both *S*-adenosylhomocysteine and As(III) (Packianathan et al., 2018b). Based on function-structure analyses with these solved crystal structures, a disulfide-bond cascade mechanism model has been proposed for the mechanism of ArsM (Marapakala et al., 2015), which explains how the product is maintained in the trivalent state during the catalytic cycle.

Although the microbial demethylation was documented (Lehr et al., 2003), molecular mechanisms of the reaction were largely unknown. Florida golf course soil, where MAs(V) had been used as herbicide and largely broken down into inorganic species, was shown to carry out MAs(V) degradation via a two-step pathway (Yoshinaga et al., 2011). The first step is reduction of MAs(V) to MAs(III) catalyzed by a *Burkholderia* isolate, while the second step is demethylation of MAs(III) to As(III) carried out by a *Streptomyces* isolate. The *arsI* gene for MAs(III)-demethylation was identified from *Bacillus* sp. MD1, another demethylating isolate from Florida golf course soil. The gene product, ArsI, is a non-heme iron dependent extradiol dioxygenase that cleaves carbon-arsenic (C-As) bond (Fig. 1B) (Yoshinaga & Rosen, 2014). Several crystal structures of TcArsI, a thermophilic ortholog from *Thermomonospora curvata*, were solved under different conditions, leading to a proposed loop-gating mechanism, where ArsI catalyzes C-As bond cleavage using a substrate-binding loop (Nadar et al., 2016). NsArsI from the freshwater cyanobacterium *Nostoc* sp. PCC 7120 was also shown to demethylate MAs(III) both *in vivo* and *in vitro* (Yan et al., 2015). It is noteworthy that cells of *Nostoc* sp. PCC 7120 demethylate not only MAs(III) but also MAs(V) into As(III), indicating that this cyanobacterium is able to reduce MAs(V) to MAs(III), the substrate of ArsI. A member of the glutathione-*S*-transferase Omega Superfamily (hGSTO1-1) from humans has been demonstrated to reduce MAs(V) to MAs(III) (Zakharyan et al., 2001), but orthologs have not been identified in microbes, suggesting that microbes rely on different mechanisms to reduce MAs(V). Recently, methanogenic archaea were demonstrated to demethylate DMAs(V) to generate methane (Chen et al., 2019a). Bottom sediments collected from coastal waters produced trimethylarsine oxide when aerobically incubated with arsenobetaine (Kaise et al., 1987). The microbes and genes involved in such degradation of DMAs(V) and production of trimethylarsine oxide remain to be isolated and characterized.

Synthesis and degradation of arsenosugars

The biosynthetic pathways for arsenosugars have not been studied well compared with those for simple methylarsenicals, probably because arsenosugars are identified mainly in marine macroalgae or animals, more complex systems than bacteria. However, the recent discovery that arsenosugars are produced by prokaryotic cyanobacteria has stimulated research on these systems (Xue et al., 2014, Xue et al., 2017a). Dimethylated arsenosugars are composed of a pentavalent dimethylarsinoy moiety and a 5′-deoxyriboside. Cells of the cyanobacterium *Synechocystis* sp. PCC 6803 produce arsenosugars when exposed to As(III), MAs(V) or DMAs(V). In contrast, cells in which the *arsM* gene was deleted produced arsenosugars only when incubated with DMAs(V), but not with either As(III) or MAs(V), suggesting that the ArsM is involved in arsenosugar biosynthesis via production of the precursor DMAs(III) (Xue et al., 2017b). In prokaryote genomes, multiple genes with related functions often form a cluster, or an operon, under the control of a single promoter. A gene adjacent to *SsarsM* (the *arsM* gene of *Synechocystis* sp. PCC 6803) has been termed *SsarsS* and is annotated to encode a radical SAM superfamily protein characterized by four iron-four sulfur ([4Fe-4S]) clusters and SAM-binding sites (Xue et al., 2019). Neither *SsarsM* nor an *SsarsS* mutant was able to produce arsenosugars, suggesting that both genes are necessary for the synthesis of arsenosugars. Recently, purified SsArsS was demonstrated to catalyze the formation of 5′-deoxy-5′-dimethylarsinoyladenosine (Table 1.23) by forming an adenosine radical (Fig. 1C) (Cheng et al., 2021). *E. coli* cells expressing both the *SsarsM* and *SsarsS* genes produced DMAs(V) and dimethylarsinoyl hydroxycarboxylic acid derivatives but not

arsenosugars, suggesting that *E. coli* cells may degrade 5′-deoxy-5′-dimethylarsinoyladenosine (Xue et al., 2019). Dimethylarsinoylalchols (DMAE and thio-DMAE), dimethylarsinoyl-carboxylic acids (DMAA and thio-DMAA), and methylarsenicals (MAs(V) and DMAs(V)) have been detected in mammalian urine and feces after ingestion of arsenosugars (Francesconi et al., 2002). Bacteria may play a role in degradation of arsenosugars in animals. In contrast, Oxo-Gly was only converted into thio-Gly in an *in vitro* artificial gastrointestinal digestion system, indicating the complexity of degradation of arsenosugars (Hata et al., 2019). Microorganisms and enzymes involved in the pathway of arsenosugar degradation remains to be identified.

Synthesis and degradation of arsenobetaine and arsenocholine

Nontoxic arsenobetaine and arsenocholine, the arsenic species primarily found in marine animals, have been considered as the end product of arsenosugar degradation (Edmonds & Francesconi, 1981). GbsB and GbsA, the enzymes encoded by the *gbsAB* glycine betaine synthetic operon from the rhizobacterium *Bacillus subtilis*, converts arsenocholine to arsenobetaine via successive oxidation reactions, where GbsB first oxidizes arsenocholine to arsenobetaine aldehyde that is subsequently oxidized to arsenobetaine by GbsA (Fig. 1D) (Hoffmann et al., 2018). In contrast, the pathway from arsenosugars to arsenocholine remains unknown. Based on arsenic species found in laboratory degradation (Foster, 2007) and feeding studies (Francesconi et al., 1989), arsenocholine has been proposed to form through the degradation of dimethylarsenoribosides (Fig. 1E), where a range of dimethylarsinoyl-hydroxycarboxylic acids (e.g. DMAA, DMAE) and the corresponding thio-arsenic compounds (e.g. thio-DMAA, thio-DMAE) are produced as intermediates. Because methylated thioarsenicals more readily interact with cysteine residues in proteins compared

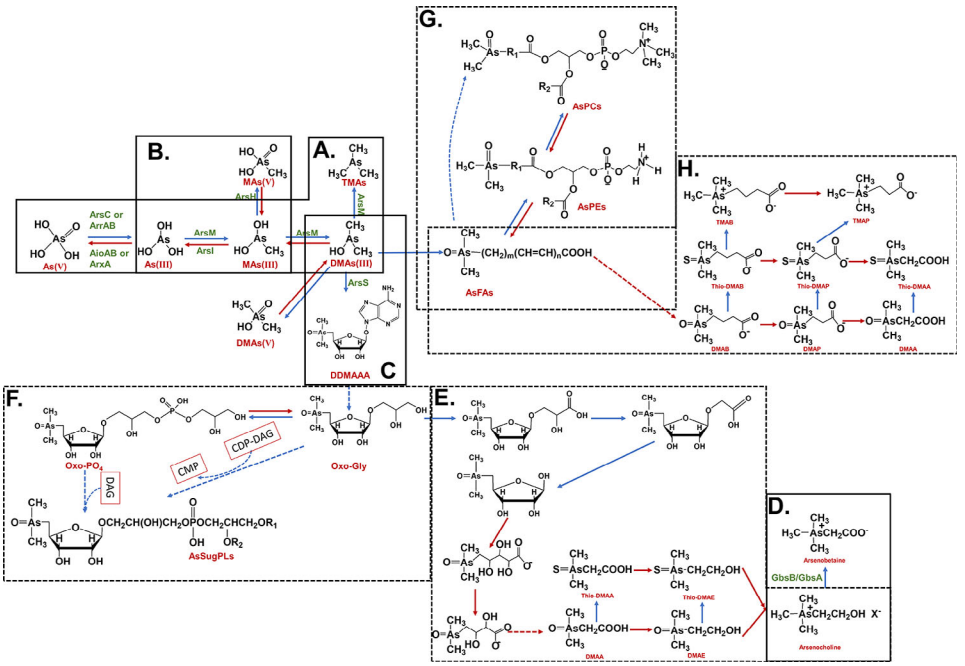


Figure 1. Proposed synthesis and degradation pathways of the organoarsenicals. A. Validated arsenic redox, methylation and demethylation pathways. B. Validated MAs(V) synthesis and degradation pathways. C. Validated synthesis pathway of the arsenosugar intermediate—DDMAA. D. Validated synthesis pathway of arsenobetaine. E. Speculated arsenocholine synthesis pathway. F. Speculated AsSugPLs synthesis pathway. G. Speculated synthesis pathways of AsPCs and AsPEs. H. Speculated AsFAs degradation pathways. Blue arrows: the synthesis pathway of the organoarsenicals, red arrows: the degradation pathway of the organoarsenicals, CDP-DAG: cytidine diphosphate-diacylglycerol, CMP: cytidine monophosphate, green words: the enzyme names, the red words: products of the different reactions, continuous lines: validated pathways, dashed lines: speculated pathways.

to the corresponding oxo arsenicals (Sun et al., 2016), thio-DMAE is considered a key precursor for arsenocholine formation, yet the formation of arsenocholine from DMAE/thio-DMAE still remains speculative. In addition, arsenobetaine has been shown to be degraded to inorganic arsenic by bacteria via the pathways [arsenobetaine→(trimethylarsine oxide)→DMAs→MAs→As(III)/As(V)] (Devesa et al., 2005). However, the pathway and molecular mechanism of arsenobetaine degradation remain to be studied.

Synthesis of arsenosugar phospholipids (AsSugPLs)

The biosynthesis of AsSugPLs is predicted to start from Oxo-Gly with or without the formation of the intermediate Oxo-PO_4 (Fig. 1F) (Zhu et al., 2017b). Diacylglycerol and cytidine diphosphate-diacylglycerol derived from phosphatidic acid serve as intermediates in the membrane phospholipid biosynthesis. Diacylglycerol is converted into phosphatidylserine, phosphatidylcholine, phosphatidylethanolamine, and phosphatidylthreonine, whereas cytidine diphosphate-diacylglycerol is a precursor for phosphatidylglycerol, phosphatidylinositol, cardiolipin, and phosphatidylserine in the prokaryotes (Jennings & Epand, 2020). However, whether AsSugPLs are synthesized from either Oxo-Gly and cytidine diphosphate-diacylglycerol or Oxo-PO_4 and diacylglycerol is not clear yet. In addition, the biosynthesis of AsSugPLs likely takes place at the outer surface of the cytoplasmic membrane, similar to lipid biosynthesis.

Synthesis and degradation of other complex arsenolipids

The non-arsenic analogs of three arsenic-containing single-chain lipids (AsHCs, AsFAs and trimethylarsenio fatty alcohols) are rare in nature. A gene cluster involved in biosynthesis of an AsFA metabolite, predicted as either dimethylarsinoyl hydroxy fatty acid or As(V)-containing fatty acid based on the mass, was identified in *Streptomyces coelicolor* and *Streptomyces lividans* (Cruz-Morales et al., 2016). The proposed biosynthesis pathway of the AsFA metabolite is based on annotations of the genes in the cluster, where the gene annotated to encode a homolog of AroA (enolpyruvyl shikimate 3-phosphate synthase) is predicted to catalyze the first step, the formation of arsenoenolpyruvate from As(V). A mutant strain lacking the *aroA* gene lost the ability to produce the AsFA metabolite, partially supporting the proposed pathway, yet the entire pathway largely remains unknown (Cruz-Morales et al., 2016).

Arsenolipids are comparable to usual non-arsenic-containing lipids in terms of both diversity and abundance, suggesting that the formation of complex arsenolipids may merely be a consequence of biochemical promiscuity. For example, AsPEs are generated likely because the cells mistakenly incorporate AsFAs into the synthetic scheme of their analogous compounds - phosphatidylethanolamines. The cells adventitiously incorporate AsFAs into the synthetic route of phosphatidylcholines or methylate AsPEs to give rise to AsPCs (Fig. 1G). A variety range of AsFAs suggest that AsFAs-containing lipids likely are from accidental incorporation, and arsenic-containing identified previously.

There have been few studies on the metabolism of arsenolipids. AsFAs have been shown to be degraded to DMAs(V) and short-chain AsFAs derivatives such as dimethylarsenopropanoic acid, 4-dimetylarsinoyl butanoic acid, dimethylarsoniothioylpropanoic acid (Table 1.57) and 4-dimethylarsinothioyl butanoic acid (Table 1.58) in humans (Fig. 1H) (Schmeisser et al., 2005), whereas AsHCs were metabolized neither in fully differentiated human brain cells (Müller et al., 2018) nor in the Caco-2 intestinal cells (Meyer et al., 2015). Phosphatidylarsenocholine administered orally to mice is mostly metabolized to arsenobetaine (Fukuda et al., 2011). AsSugPLs are degraded more readily than long-chain AsHCs in decomposing brown kelp *Ecklonia Radiata* (Glabonjat et al., 2019a). *Caenorhabditis elegans*, which barely degrades either AsFAs or AsTAGs, substantially metabolized AsHCs to thiolated AsHCs or shortened AsFAs metabolites, suggesting

that AsHCs are partially oxidized to AsFAs and in turn degraded via β-oxidation (Bornhorst et al., 2020).

Inorganic arsenic and organoarsenicals are in dynamic equilibrium in the biosphere, some organisms synthesize simple or complex organoarsenicals in order to detoxify inorganic arsenicals or utilize organoarsenicals. However, these organoarsenicals may be toxic to other organisms that cannot produce them, and will be degraded by these organisms or microbes in their body.

Toxicity of organoarsenicals

Toxicity of methylated arsenic

Arsenic methylation is widely considered a detoxification process because it ultimately converts arsenic into much less toxic pentavalent methylated species (e.g. MAs(V) and DMAs(V)) after oxidation in air. Yet the actual products are trivalent species (e.g. MAs(III) and DMAs(III)) that are much more toxic than inorganic arsenic (Table S9). The trivalent methylarsenicals have a profound impact on cell viability or proliferation via a) inhibiting activities of key enzymes, b) damaging DNA structure, and c) activating the transcription factor activator protein-1, which is involved in cellular proliferation, transformation and death (Soza-Ried et al., 2019). MAs(III) has antibiotic-like properties, suggesting that arsenic methylation may have originally evolved as an offensive weapon (Chen et al., 2019b). MAs(III) achieves the potent antimicrobial effect through the robust affinity with thiols in essential enzymes for carbohydrate metabolism such as glycerol-3-phosphate dehydrogenase (Lee & Levin, 2019), pyruvate dehydrogenase and α-ketoglutarate dehydrogenase (Tokmina-Lukaszewska et al., 2017), and redox-regulating small proteins/molecules such as glutaredoxin/thioredoxin and glutathione (Shen et al., 2013). MAs(III) was recently shown to inhibit MurA, an essential enzyme in bacterial cell wall biosynthesis (Garbinski et al., 2020). Bacteria develop resistance to MAs(III) via three types of enzymes, a) the C–As lyase ArsI degrades MAs(III) into As(III) (Yoshinaga & Rosen, 2014), b) the flavoprotein ArsH uses $NADP^+$ to oxidize MAs(III) to MAs(V) (Chen et al., 2015b), c) the MAs(III) efflux permease ArsP extrudes MAs(III) out of cells (Chen et al., 2015a). MAs(III) and DMAs(III) are highly cytotoxic and genotoxic to human cells than their pentavalent counterparts and inorganic arsenic (Dopp et al., 2010), although the toxicity may depend on the cell types and exposure conditions. Thio-pentavalent arsenic species showed higher partition coefficients, suggesting that they can easily traverse cell membranes by passive simple diffusion, which gives higher toxicity of these species compared to oxo-pentavalent arsenic species (Chávez-Capilla et al., 2016). Thio-dimethylarsinic acid was more potent than As(III) as an inhibitor of the ribosylation of poly-adenosine diphosphate that is induced by DNA damage (Ebert et al., 2014). Moreover, the cytotoxic effects of thio-DMA may in part be associated with an apoptotic mode of cell death (Ochi et al., 2008).

In air, MAs(III) and DMAs(III) are oxidized to MAs(V) and DMAs(V). However, flowering plants do not methylate arsenic, rather they take up methylarsenicals produced by microbes (Yang et al., 2018. Accumulation of DMAs(V) in the caryopsis of rice before flowering results in markedly reduced grain yield, likely because of higher toxicity of DMAs(V) to the reproductive tissues (Zheng et al., 2011). DMAs(V) prevents expression of genes related to cell wall modification and oxidative stress responses in rice, leading to straight head disease (Tang et al., 2020). Dimethylmonothioarsinic acid (Table 1.10) significantly increased arsenic accumulation in rice grains either as DMAs(V) or partially as dimethylmonothioarsinic acid (Kerl et al., 2019).

Toxicity of arsenosugars

Arsenosugars and their metabolites have been supposed to be toxic (Feldmann & Krupp, 2011). Oxo-Gly and Oxo-SO_4 exerted neither cytotoxicity nor genotoxicity even at the millimolar

concentrations (Andrewes et al., 2004). Oxo-Gly, as well as the other organoarsenicals such as trimethylarsine oxide, tetramethylarsonium ion, arsenocholine and arsenobetaine, induced only minor chromosomal aberrations in human fibroblasts at relatively high concentrations (Table S9). Although trivalent Oxo-Gly was more cytotoxic to human epidermal keratinocytes *in vitro* than its pentavalent counterpart, both were clearly less toxic than DMAs(III), MAs(III), or As(V) (Andrewes et al., 2004). Among the arsenosugar metabolites, thio-DMAs(V) and thio-DMAE, showed high bioavailability in a Caco-2 intestinal barrier model, which was similar to As(III), and thio-DMAs(V) exerted much higher cellular toxicity than As(III), likely because of generation of more toxic DMAs(III) (Leffers et al., 2013). In contrast, the arsenosugar metabolites DMAA, thio-DMAA and DMAE showed low intestinal bioavailability, comparable to MAs(V) and DMAs(V) (Calatayud et al., 2012; Leffers et al., 2013). Taken together, the cytotoxicity of arsenosugars and their metabolites may be comparable with inorganic arsenic. However, the permeability of MAs(V) and DMAs(V) increased significantly in Caco-2/HT29-MTX co-cultures compared with the Caco-2 monoculture (Calatayud et al., 2012).

Toxicity of arsenolipids

Recently, lipid-soluble organoarsenicals have attracted interests in relation to human health as more diverse arsenolipids have been shown to be present at high concentrations in many edible seafood. Among the tested arsenolipids, only AsHCs have been shown to be toxic to animals and humans (Table S9). AsHCs with hydrophobic hydrocarbon tail possess the ability to pass the *in vitro* Caco-2 intestinal barrier of humans (Meyer et al., 2015) and the blood-brain barrier of the fruit fly *Drosophila melanogaster* (Niehoff et al., 2016), and can be transported into the milk of nursing mothers after fish consumption (Xiong et al., 2020). AsHCs with high bioavailability (AsHC 332 and AsHC 360) nearly completely inhibited the hatching of fruit flies from pupae, whereas AsHC444 with lower bioavailability exerted relatively less developmental toxicity to *D. melanogaster* than both AsHC 332 and AsHC 360 (Meyer et al., 2014a). AsHCs showed significant cytotoxic to the UROtsa (human urothelium) and HepG2 (human liver) cells by disturbing the cell membrane integrity and decreasing level of energy related nucleotides (Meyer et al., 2014b), and thio-AsHC 348 (thiolate AsHC 332) was at least as cytotoxic as the oxo parent compound (AsHC 332) but likely acts via a different mode (Ebert et al., 2020). In addition, AsHCs massively disturbed the neuronal network and induced apoptosis in differentiated human brain cells (Witt et al., 2017b), and exerted pronounced neurodevelopmental effects on pre-differentiated human neurons (Witt et al., 2017a). In contrast, AsFAs or their minor water-soluble metabolites (Oxo/thio- dimethylarsenopropanoic acid) did not exhibit any adverse effects to differentiated neurons (Witt et al., 2017b), or Caco-2 cells (Meyer et al., 2015). The toxicity of AsPC 839 and its hydrolysis products was less pronounced than AsHCs or inorganic arsenic (Finke et al., 2020).

Others

SAM is a common substrate involved in numerous biosynthetic pathways, including posttranslational modifications, synthesis of protein cofactors, DNA methylation, and synthesis of the non-protein ligands by generating a central 5′-dAdo• radical, methyl radical, or 3-amino-3-carboxypropyl radical intermediate (Broderick et al., 2014). The availability of SAM in cells may be disturbed by the synthesis of organoarsenicals including methylated arsenicals (Qin et al., 2006), arsinothricin (Suzol et al., 2020), and arsenosugars (Xue et al., 2017b). In humans, arsenic perturbation of SAM metabolism may lead to cancer by producing epigenetic modifications and by disrupting the expression of miRNAs (Soza-Ried et al., 2019). Organoarsenicals and their metabolic pathways may exert an adverse effect on growth, with some exceptions such as arsenobetaine, the

arsenic compound with the lowest toxicity (Table S9), which is excreted unchanged by the human kidney.

Potential functions of organoarsenicals

Potential functions of methylated arsenicals

Little is known about the biological or ecological functions of organoarsenicals, except arsenic methylation that is demonstrated to serve as a mechanism of antibiotic production, as a detoxification process or as a step in the biosynthesis of more complex organoarsenicals such as arsenosugars. Environmental arsenic enters cells adventitiously via transport systems for essential nutrients that are unable to distinguish arsenic from their actual substrates. As(V) competes with phosphate, inhibiting alkylation, acylation or phosphorylation reactions, leading to futile cycles of synthesis and breakdown of extremely unstable compounds such as organoarsenical 1-arseno-3-phosphoglycerate, which has a half-life of only a few seconds (Chen et al., 2016; Rosen et al., 2011). As(III) has high affinity for thiol groups in proteins and small molecules (Shen et al., 2013). Arsenic-sulfur bond formation inhibits a number of biochemical reactions. Pentavalent MAs(V), DMAs(V) and trimethylarsine oxide are less toxic than As(III). In addition, the uptake efficiency of organisms for pentavalent methylated arsenic is generally very low, although mechanisms for uptake of methylated arsenicals have been identified (Chen et al., 2016).

Biological functions of arsenobetaine

Arsenobetaine functions as an effective osmostress protectant similar to the nitrogen analog glycine betaine. For example, the blue mussel *M. edulis* does not metabolize arsenobetaines (Francesconi et al., 1999), but rather accumulates it in response to an increase in salinity (Clowes & Francesconi, 2004). Arsenic speciation in the mushrooms of 46 different fungus species over a diverse range of phylogenetic groups demonstrated that mushrooms with puffball or gilled morphologies all contain high proportion of arsenobetaine, suggesting that arsenobetaine may act as an osmolyte in some mushrooms to maintain the structure of the fruiting body (Nearing et al., 2014). Recently, *B. subtilis* was demonstrated to rely on biosynthetic enzymes, genetic regulatory circuits and uptake systems for glycine betaine to accumulate arsenobetaine either via uptake or synthesis from the precursor arsenocholine to utilize it as osmolytes. It strongly suggests a function of arsenobetaine against high osmolarity and extreme growth temperature (Hoffmann et al., 2018).

Potential functions of arsenosugars and arsenosugar phospholipids

We previously showed that cyanobacteria have a key enzyme for biosynthesis of arsenosugars, which are the immediate precursors for AsSugPLs (Xue et al., 2019), yet the functions of arsenosugars and AsSugPLs are not well understood. Reducing intracellular arsenic by sequestration is not likely the primary role of AsSugPLs, given that algae have increased AsSugPLs synthesis under abiotic stress conditions (Pétursdóttir et al., 2016). Growth under oxidative stress and low phosphate resulted in the synthesis of significantly more AsSugPLs in strains of the filamentous brown alga *Ectocarpus* genus. Under low phosphate conditions, the amounts of Oxo-PO_4 produced were significantly reduced, and the amounts of AsSugPLs were significantly increased (Pétursdóttir et al., 2016), suggesting that AsSugPLs play a more fundamental, pro-active role in the organism's growth or resistance to environmental stress.

Potential functions of other arsenolipids

Lipids are a chemically diverse group of compounds that perform various functions. Neutral lipids triacylglycerol and diacylglycerol are the principal stored forms of energy in cells. Polar lipids such as phosphatidylcholine, phosphatidylethanolamine, phosphatidylglycerol, phosphatidylserine, phosphatidylinositol, phosphatidic acid, sphingolipids, and archaeal ether lipids are major structural elements of biological membranes. Ceramide and its derivatives are involved in regulation of cell division, differentiation, migration and apoptosis (Latner, 1970). Ninety eight AsFA-containing lipids have been identified in green alga *Coccomyxa* species (Řezanka et al., 2019), raising the questions of whether these arsenolipids have functions similar to their lipid analogs. The roles of arsenic in evolution may be more than imagined. As(III)-based anoxygenic photosynthesis would have been an ancient process in altering the Earth's environment from highly to moderately reducing (Oremland et al., 2009). More recently, channel mats found in Laguna La Brava, a hypersaline lake in the Salar de Atacama of northern Chile, were demonstrated to form "arsenotrophic" microbial communities that support arsenic and sulfur cycling coupled to anoxygenic photosynthesis (carbon fixation) and anaerobic respiration (organic carbon decomposition) under completely anoxic conditions (Visscher et al., 2020). The future discovery of organisms that rely on arsenic, such as arsenosugars/AsSugPLs-producing cyanobacteria that are capable of As(III)-based anoxygenic photosynthesis, would suggest roles for arsenic in primordial life. The discovery of AsSugPhytols containing 2-*O*-methylriboside, which previously had been only found in RNA and methyl-RNA and considered as the evolutionary bridge between RNA and DNA (Poole et al., 2000), supports our speculation about a biological role of arsenic in the first organisms (Glabonjat et al., 2017).

Perspectives

Given the extraordinary complexity of naturally occurring arsenic species, the future in understanding of its biogeochemistry will be reliant on the collaboration between wide range of disciplines. We propose that the following topics are of general interest and worth further in-depth investigations.

MAs(III) has been shown to have antimicrobial properties (Chen et al., 2019b) through the robust affinity with thiols in essential enzymes and redox-regulating small proteins/molecules. Arsinothricin inhibits both Gram-negative and Gram-positive bacteria growth (Nadar et al., 2019). As a chemical mimetic of the acylphosphate intermediate in the glutamine synthetase reaction, arsinothricin specifically binds to the active site of glutamine synthetase and inhibits the enzyme. But is that its only mechanism of action? Are there other arsenic-containing compounds having antimicrobial properties? The abundance of antibiotic resistance genes has increased with the widespread use of antibiotics (Zhu et al., 2017a). What is the effect of environmental arsenic-containing compounds on the abundance and transfer of antibiotic resistance genes? Arsenic resistance genes often cluster with antibiotic resistance genes, so environmental arsenic can spread associated antibiotic resistances by lateral gene transfer (Pal et al., 2015). Metagenomics can be used to study the effect of arsenic-containing compounds on the spread of antibiotic resistance genes.

Over 260 arsenolipids have been identified following improvements in analytical methods, the vast majority of which are AsFA-containing compounds. It is likely that lipid biosynthetic enzymes mistakenly incorporate AsFAs and produce the AsFA-containing lipids. Future research should focus on the synthesis and degradation of arsenolipids, as well as their potential biological and ecological consequences. What are the structural differences between enzymes of lipid synthesis from organisms that produce arsenolipids and from those that do not synthesize arsenolipids? The identification, purification, and characterization of enzymes involved in arsenolipid synthesis in microorganisms should be intensively investigated. Most of the identified arsenolipids are

found in marine organisms, are arsenolipids also widely distributed in terrestrial biota, if so, then are the arsenolipids produced by environmental microbes or higher and/or larger organisms? The presence of arsenolipids in a wide range of terrestrial biota (including microbes) should be examined. In addition, do arsenolipids serve as lipid analogs (Foster, 2007)? Are arsenolipids generally distributed in the bilayer of membranes or in microdomains? Do the nontoxic arsenolipids made by marine algae or cyanobacteria have physiological roles? The distribution of arsenolipids in organisms should be studied under extreme conditions (extreme growth temperature, poor nutrition, high osmolarity, etc.) to reveal the potential biological function and the possible physiological roles. Certain microbes utilize arsenic for energy production via dissimilatory As(V) reduction and chemolithotrophic and phototrophic As(III) oxidation (Kulp et al., 2008; Oremland & Stolz, 2003). Moreover, As(V) reduction was recently found to be coupled with anaerobic methane oxidation (Shi et al., 2020). Are arsenolipids also coupled with energy production or the biogeochemical cycling of other elements?

Recently, significant interest has been focused on the gut microbiome, which is linked to digestion, host metabolism, energy production, immune cell development, homeostasis, and human diseases (Capuco et al., 2020; Little et al., 2020; Trøseid et al., 2020). On one hand, the gut microbiome makes a significant contribution to arsenic speciation in the earthworm (Wang et al., 2019a, Wang et al., 2019b) and mice gut (Lu et al., 2013). On the other hand, arsenic metabolism by the gut microbiome may affect host reproduction and metabolism (Chi et al., 2019; Zhou et al., 2020). Taking into account the essential role of the gut microbiota in arsenic transformation and in human disorders, the following questions arise: (1) Which species of gut microbiota are involved in the degradation/transformation of organoarsenicals? (2) How do organoarsenicals and their degradation products affect the community structure of the gut microbiome? (3) What is the effect of an altered gut microbiome on human health? The simulator of the human intestinal microbial ecosystem with microbial communities from different populations (Van de Wiele et al., 2015) and the *in vivo* animal model (earthworm, mice, etc.) will help solve the reaction between organoarsenical metabolism and microbial community structure. The comparisons of gut microbiota compositions between organoarsenical-feed and non-organoarsenical-feed should be conducted, the long-time impact of organoarsenicals on gut microbiota activity and community should be studied, and the metabolites of organoarsenicals produced by gut microbiota should be assessed for their potential toxicity on human health.

The slow progress in the metabolism/toxicity study on organoarsenicals, especially the arsenolipids was due to its rich diversity, complex structure, and the shortness of standard materials. Therefore, some simple and efficient separation and purification technologies need to be developed to prepare standard organoarsenical materials that can be used for metabolism/toxicology research in the future. In addition to *in vitro* models, animal models should be further explored, with a special focus on the metabolic process and the metabolites (especially thio-organoarsenicals) in mammals. Furthermore, system approaches to characterizing the impact of organoarsenicals on human health should be developed and applied in risk assessment.

In summary, continual improvements in modern analytical techniques will lead to identification of additional simple or complex organoarsenicals. However, fundamental questions about their occurrence, prevalence and fate in the environment, synthesis and degradation, toxicology, biological and ecological functions remain largely unanswered. This review will provide new direction for future research in the field of environmental organoarsenicals.

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